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(57) Abstract

The present invention relates to methods for treating fungal infection comprising administering to a subject suffering from a fungal infection a bactericidal/permeability-inducing (BPI) protein product.

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ANTI-FUNGAL METHODS AND MATERIALS

This is a continuation-in-part of U.S. Patent Application Serial No. 08/273,540 filed July 11, 1994, which is a continuation-in-part of U.S. Patent Application Serial No. 08/209,762 filed March 11, 1994, which is a continuation-in-part of U.S. Patent Application Serial No. 08/183,222 filed January 14, 1994, all of which are herein incorporated by reference.

BACKGROUND OF THE INVENTION

The present invention relates generally to methods of treating fungal infections by administration of bactericidal/permeability-increasing (BPI) protein products.

BPI is a protein isolated from the granules of mammalian polymorphonuclear leukocytes (PMNs or neutrophils), which are blood cells essential in the defense against invading microorganisms. Human BPI protein has been isolated from PMNs by acid extraction combined with either ion exchange chromatography [Elsbach, *J. Biol. Chem.*, *254*:11000 (1979)] or *E. coli* affinity chromatography [Weiss, et al., *Blood*, *69*:652 (1987)]. BPI obtained in such a manner is referred to herein as natural BPI and has been shown to have potent bactericidal activity against a broad spectrum of gram-negative bacteria. The molecular weight of human BPI is approximately 55,000 daltons (55 kD). The amino acid sequence of the entire human BPI protein and the nucleic acid sequence of DNA encoding the protein have been reported in Figure 1 of Gray et al., *J. Biol. Chem.*, *264*:9505 (1989), incorporated herein by reference. The Gray et al. amino acid sequence is set out in SEQ ID NO: 69 hereto.

BPI is a strongly cationic protein. The N-terminal half of BPI accounts for the high net positive charge; the C-terminal half of the molecule has a net charge of -3. [Elsbach and Weiss (1981), *supra*.] A proteolytic N-terminal fragment of BPI having a molecular weight of about 25 kD has an amphipathic character, containing alternating hydrophobic and hydrophilic regions. This N-terminal fragment of human BPI possesses the anti-bacterial efficacy of the naturally-derived 55 kD human BPI holoprotein. [Ooi et al., *J. Bio. Chem.*, *262*:

14891-14894 (1987)]. In contrast to the N-terminal portion, the C-terminal region of the isolated human BPI protein displays only slightly detectable anti-bacterial activity against gram-negative organisms. [Ooi et al., *J. Exp. Med.*, *174*:649 (1991).] An N-terminal BPI fragment of approximately 23 kD, referred to as "$rBPI_{23}$," has been produced by recombinant means and also retains anti-bacterial activity against gram-negative organisms. Gazzano-Santoro et al., *Infect. Immun. 60*:4754-4761 (1992).

The bactericidal effect of BPI has been reported to be highly specific to gram-negative species, e.g., in Elsbach and Weiss, *Inflammation: Basic Principles and Clinical Correlates*, eds. Gallin et al., Chapter 30, Raven Press, Ltd. (1992). BPI is commonly thought to be non-toxic for other microorganisms, including yeast, and for higher eukaryotic cells. Elsbach and Weiss (1992), *supra*, reported that BPI exhibits anti-bacterial activity towards a broad range of gram-negative bacteria at concentrations as low as 10^{-8} to 10^{-9} M, but that 100- to 1,000-fold higher concentrations of BPI were non-toxic to all of the gram-positive bacterial species, yeasts, and higher eukaryotic cells tested at that time. It was also reported that BPI at a concentration of 10^{-6} M or 160 μg/ml had no toxic effect, when tested at a pH of either 7.0 or 5.5, on the gram-positive organisms *Staphylococcus aureus* (four strains), *Staphylococcus epidermidis*, *Streptococcus faecalis*, *Bacillus subtilis*, *Micrococcus lysodeikticus*, and *Listeria monocytogenes*. BPI at 10^{-6} M reportedly had no toxic effect on the fungi *Candida albicans* and *Candida parapsilosis* at pH 7.0 or 5.5, and was non-toxic to higher eukaryotic cells such as human, rabbit and sheep red blood cells and several human tumor cell lines. See also Elsbach and Weiss, *Advances in Inflammation Research*, ed. G. Weissmann, Vol. 2, pages 95-113 Raven Press (1981). This reported target cell specificity was believed to be the result of the strong attraction of BPI for lipopolysaccharide (LPS), which is unique to the outer membrane (or envelope) of gram-negative organisms.

The precise mechanism by which BPI kills gram-negative bacteria is not yet completely elucidated, but it is believed that BPI must first bind to the surface of the bacteria through electrostatic and hydrophobic interactions between

the cationic BPI protein and negatively charged sites on LPS. LPS has been referred to as "endotoxin" because of the potent inflammatory response that it stimulates, i.e., the release of mediators by host inflammatory cells which may ultimately result in irreversible endotoxic shock. BPI binds to lipid A, reported to be the most toxic and most biologically active component of LPS.

In susceptible gram-negative bacteria, BPI binding is thought to disrupt LPS structure, leading to activation of bacterial enzymes that degrade phospholipids and peptidoglycans, altering the permeability of the cell's outer membrane, and initiating events that ultimately lead to cell death. [Elsbach and Weiss (1992), *supra*]. BPI is thought to act in two stages. The first is a sublethal stage that is characterized by immediate growth arrest, permeabilization of the outer membrane and selective activation of bacterial enzymes that hydrolyze phospholipids and peptidoglycans. Bacteria at this stage can be rescued by growth in serum albumin supplemented media [Mannion et al., *J. Clin. Invest.*, *85*:853-860 (1990)]. The second stage, defined by growth inhibition that cannot be reversed by serum albumin, occurs after prolonged exposure of the bacteria to BPI and is characterized by extensive physiologic and structural changes, including apparent damage to the inner cytoplasmic membrane.

Initial binding of BPI to LPS leads to organizational changes that probably result from binding to the anionic groups in the KDO region of LPS, which normally stabilize the outer membrane through binding of Mg^{++} and Ca^{++}. Attachment of BPI to the outer membrane of gram-negative bacteria produces rapid permeabilization of the outer membrane to hydrophobic agents such as actinomycin D. Binding of BPI and subsequent gram-negative bacterial killing depends, at least in part, upon the LPS polysaccharide chain length, with long O-chain bearing, "smooth" organisms being more resistant to BPI bactericidal effects than short O-chain bearing, "rough" organisms [Weiss et al., *J. Clin. Invest. 65*: 619-628 (1980)]. This first stage of BPI action, permeabilization of the gram-negative outer envelope, is reversible upon dissociation of the BPI, a process requiring the presence of divalent cations and synthesis of new LPS [Weiss et al., *J. Immunol. 132*: 3109-3115 (1984)]. Loss of gram-negative

bacterial viability, however, is not reversed by processes which restore the envelope integrity, suggesting that the bactericidal action is mediated by additional lesions induced in the target organism and which may be situated at the cytoplasmic membrane (Mannion et al., *J. Clin. Invest. 86*: 631-641 (1990)). Specific investigation of this possibility has shown that on a molar basis BPI is at least as inhibitory of cytoplasmic membrane vesicle function as polymyxin B (In't Veld et al., *Infection and Immunity 56*: 1203-1208 (1988)) but the exact mechanism as well as the relevance of such vesicles to studies of intact organisms has not yet been elucidated.

Fungi are eukaryotic cells that may reproduce sexually or asexually and may be biphasic, with one form in nature and a different form in the infected host. Fungal diseases are referred to as mycoses. Some mycoses are endemic, i.e. infection is acquired in the geographic area that is the natural habitat of that fungus. These endemic mycoses are usually self-limited and minimally symptomatic. Some mycoses are chiefly opportunistic, occurring in immunocompromised patients such as organ transplant patients, cancer patients undergoing chemotherapy, burn patients, AIDS patients, or patients with diabetic ketoacidosis.

Fungal infections are becoming a major health concern for a number of reasons, including the limited number of anti-fungal agents available, the increasing incidence of species resistant to older anti-fungal agents, and the growing population of immunocompromised patients at risk for opportunistic fungal infections. The incidence of systemic fungal infections increased 600% in teaching hospitals and 220% in non-teaching hospitals during the 1980's. The most common clinical isolate is *Candida albicans* (comprising about 19% of all isolates). In one study, nearly 40% of all deaths from hospital-acquired infections were due to fungi. [Sternberg, *Science*, 266:1632-1634 (1994).]

Anti-fungal agents include three main groups. The major group includes polyene derivatives, including amphotericin B and the structurally related compounds nystatin and pimaricin. These are broad-spectrum anti-fungals that bind to ergosterol, a component of fungal cell membranes, and thereby disrupt

the membranes. Amphotericin B is usually effective for systemic mycoses, but its administration is limited by toxic effects that include fever and kidney damage, and other accompanying side effects such as anemia, low blood pressure, headache, nausea, vomiting and phlebitis. The unrelated anti-fungal agent flucytosine (5-fluorocytosine), an orally absorbed drug, is frequently used as an adjunct to amphotericin B treatment for some forms of candidiasis and cryptococcal meningitis. Its adverse effects include bone marrow depression with leukopenia and thrombocytopenia.

The second major group of anti-fungal agents includes azole derivatives which impair synthesis of ergosterol and lead to accumulation of metabolites that disrupt the function of fungal membrane-bound enzyme systems (e.g., cytochrome P450) and inhibit fungal growth. Significant inhibition of mammalian P450 results in significant drug interactions. This group of agents includes ketoconazole, clotrimazole, miconazole, econazole, butoconazole, oxiconazole, sulconazole, terconazole, fluconazole and itraconazole. These agents may be administered to treat systemic mycoses. Ketoconazole, an orally administered imidazole, is used to treat nonmeningeal blastomycosis, histoplasmosis, coccidioidomycosis and paracoccidioidomycosis in non-immunocompromised patients, and is also useful for oral and esophageal candidiasis. Adverse effects include rare drug-induced hepatitis; ketoconazole is also contraindicated in pregnancy. Itraconazole appears to have fewer side effects than ketoconazole and is used for most of the same indications. Fluconazole also has fewer side effects than ketoconazole that is used for oral and esophageal candidiasis and cryptococcal meningitis. Miconazole is a parenteral imidazole with efficacy in coccidioidomycosis and several other mycoses, but has side effects including hyperlipidemia and hyponatremia.

The third major group of anti-fungal agents includes allylamines-thiocarbamates, which are generally used to treat skin infections. This group includes tolnaftate and naftifine.

Another anti-fungal agent is griseofulvin, a fungistatic agent which is administered orally for fungal infections of skin, hair or nails that do not respond to topical treatment.

Most endemic mycoses are acquired by the respiratory route and are minimally symptomatic; cough, fever, headache, and pleuritic pain may be seen. Occasionally, endemic mycoses may cause progressive pulmonary disease or systemic infection. Histoplasmosis, caused by *Histoplasma*, is the most common endemic respiratory mycosis in the United States; over 40 million people have been infected. The disease is noncontagious and ordinarily self-limited, but chronic pulmonary infection and disseminated infection may occur. Pulmonary infection rarely requires treatment, but disseminated infection may be treated with amphotericin B. Coccidioidomycosis, caused by *Coccidioides*, is a noncontagious respiratory mycosis prevalent in the southwest. It also is usually self-limited but may lead to chronic pulmonary infection or disseminated infection. Amphotericin B or miconazole may be given for treatment. Blastomycosis, caused by *Blastomyces* is a noncontagious, subacute or chronic endemic mycosis most commonly seen in the southeast. Most pulmonary infections are probably self-limited. Patients with progressive lung disease or disseminated disease, and immunocompromised patients, may be treated systemically with amphotericin B. Paracoccidioidomycosis, caused by *Paracoccidioides*, is a noncontagious respiratory mycosis that is the most common systemic mycosis in South America. It may be acute and self-limited or may produce progressive pulmonary disease or extrapulmonary dissemination. Disseminated disease is generally fatal in the absence of therapy. Sulfonamides may be used but have a low success rate. Amphotericin B produces a higher response rate but relapses may still occur.

Cryptococcosis is a noncontagious, often opportunistic mycosis. It is characterized by respiratory involvement or hematogenous dissemination, often with meningitis. A major etiologic agent is *C. neoformans*. Most pulmonary infections are probably overlooked, but cryptococcal meningitis, which accounts for 90% of reported disease, is dramatic and seldom overlooked. Cryptococcosis is a particular problem in immunocompromised patients;

cryptococcal meningitis occurs in 7 to 10% f AIDS patients. The principal symptom of meningitis is headache; associated findings include mental changes, ocular symptoms, hearing deficits, nausea, vomiting, and seizures. Without treatment, 80% of patients die within two years. In meningitis, cryptococci can be observed in India ink preparations of cerebrospinal fluid sediment, and can be cultured from the cerebrospinal fluid. Treatment is generally with fluconazole or the combination of amphotericin B and flucytosine, although amphotericin B does not cross the blood brain barrier.

Aspergillosis is a term that encompasses a variety of disease processes caused by *Aspergillus* species. *Aspergillus* species are ubiquitous; their spores are constantly being inhaled. Of the more than 300 species known, only a few are ordinarily pathogenic for man: *A. fumigatus*, *A. flavus*, *A. niger*, *A. nidulans*, *A. terreus*, *A. sydowi*, *A. flavanus*, and *A. glaucus*. Aspergillosis is increasing in prevalence and is particularly a problem among patients with chronic respiratory disease or immunocompromised patients. Among immunocompromised patients, aspergillosis is second only to candidiasis as the most common opportunistic mycosis and accounts for about 15% of the systemic mycoses in this group. Opportunistic pulmonary aspergillosis is characterized by widespread bronchial erosion and ulceration, followed by invasion of the pulmonary vessels, with thrombosis, embolization and infarction. Clinically, infection manifests as a necrotizing patchy bronchopneumonia, sometimes with hemorrhagic pulmonary infarction. In about 40% of cases, there is hematogenous spread to other sites. Aspergillosis is also a rare but devastating complication of burn wounds; amputation is often required for cure. Invasive aspergillosis is commonly fatal, so aggressive diagnosis and treatment is required. Blood, urine and cerebrospinal fluid cultures are rarely positive, but fungi can be seen in smears and biopsies. Amphotericin B can be given for treatment.

Mucormycosis is an acute suppurative opportunistic mycosis that produces rhinocerebral, pulmonary or disseminated disease in immunocompromised patients, and local or disseminated disease in patients with burns or open wounds. Infection is caused by fungi in the class Zygomycetes,

and include *Basidiobolus*, *Conidiobolus*, *Rhizopus*, *Mucor*, *Absidia*, *Mortierella*, *Cunninghamella*, and *Saksenaea*. Rhinocerebral mucormycosis accounts for about half of all cases of mucormycosis. It is one of the most rapidly fatal fungal diseases, with death occurring within 2-10 days in untreated patients. Early clinical signs include nasal stuffiness, bloody nasal discharge, facial swelling and facial pain. The infection then spreads to the eyes, cranial nerves and brain. Pulmonary mucormycosis is nearly as common as rhinocerebral disease and manifests with the same necrotizing and infarction as aspergillosis. Fungi are virtually never seen or cultured from blood, sputum or cerebrospinal fluid. Disseminated mucormycosis may follow pulmonary or burn wound infection. Treatment is with amphotericin B.

Candidiasis is a general term for a variety of local and systemic processes caused by colonization or infection of the host by species of the yeast *Candida*. Candidiasis occurs worldwide; superficial infections of the skin, mouth and other mucus membranes are universal. Invasive systemic disease has become a problem due to the use of high doses of antibiotics that destroy normal bacterial flora, immunosuppressive agents, and agents toxic to bone marrow, *e.g.*, during cancer therapy. Neutropenia is a major risk factor for *Candida* dissemination. Candidiasis is also seen among immunocompromised individuals such as AIDS patients, organ transplant patients, patients receiving parenteral nutrition, and cancer patients undergoing radiation treatment and chemotherapy. It is the most common opportunistic mycosis in the world. The most common etiologic agent is *Candida albicans*. Other infectious species include *C. tropicalis*, *C. parapsilosis*, *C. stellatoidea*, *C. krusei*, *C. parakrusei*, *C. lusitanae*, *C. pseudotropicalis*, *C. guilliermondi* and *C. glabrata*. *Candida albicans* is normally found in the mouth, throat, gastrointestinal tract and vagina of humans. Non-*albicans* species frequently colonize skin. *Candida* species occur in two forms that are not temperature- or host-dependent. The usual colonizing form are yeasts that may assume a pseudomycelial configuration, especially during tissue invasion. Pseudomyceliae result from the sequential budding of yeasts into branching chains of elongated organisms.

Candida albicans contains cell wall mannoproteins that appear to be responsible for attachment of the yeast cells to specific host tissues. It has been reported that the mannan portion, rather than the protein portion, of the mannoproteins is responsible for adherence of fungal cells to spleen and lymph node tissues in mice. [Kanbe et al., *Infection Immunity, 61*:2578-2584 (1993).]

C. albicans also binds avidly to extracellular matrix (ECM) proteins such as fibronectin, laminin, and types I and IV collagen, all of which contain heparin-binding domains. This suggests *C. albicans* may express a heparin-like surface molecule. Adherence of *C. albicans* to the ECM may be important in the pathogenesis of disseminated candidiasis. It has been demonstrated that heparin, heparan sulfate and dextran sulfate glycosaminoglycans (GAGs) inhibit adherence of *C. albicans* to ECM and ECM proteins, possibly by a mechanism involving binding of GAGs to ECM proteins, thus masking these selective ligands. [Klotz et al., *FEMS Microbiology Letters, 78*:205-208 (1992).]

Clinically, candidiasis manifests as superficial mucocutaneous infections, chronic mucocutaneous candidiasis, or systemic infection. Superficial mucocutaneous infections can occur in any area of skin or mucus membrane. Thrush, commonly seen in AIDS patients, is characterized by a patchy or continuous, creamy to gray pseudomembrane that covers the tongue, mouth, or other oropharyngeal surfaces and may be accompanied by ulceration and necrosis. Laryngeal involvement results in hoarseness. Esophagitis is often an extension of oropharyngeal disease and may manifest with symptoms of retrosternal pain and dysphagia. Intestinal candidiasis is commonly asymptomatic, but is a major source of hematogenous invasion in immunocompromised individuals. Intertrigo involves the axillae, groins, inframammary folds, and other warm, moist areas, and may manifest as red, oozing or dry, scaly lesions. Infections may occur in other areas, including perianal and genital areas. Paronychia, infection of the nails, often follows chronic exposure of the hands or feet to moisture. Some patients with limited T-cell immunodeficiency develop chronic mucocutaneous candidiasis. These patients suffer from persistent superficial *Candida* infection of the skin, scalp, nails and mucus membranes.

Most cases of systemic candidiasis are caused by *Candida albicans* and *C. tropicalis*, and increasingly, *C. glabrata*. Clinical manifestations of *Candida* infection appear mainly in the eyes, kidneys and skin. In the eyes, there may be single or multiple raised, white, fluffy chorioretinal lesions. These lesions are a potential cause of blindness. Involvement of the kidneys includes diffuse abscesses, capillary necrosis and obstruction of the ureters. Infection may result in progressive renal insufficiency. Systemic *Candida* infection can also manifest as maculonodular skin lesions surrounded by a reddened area; these lesions have an appearance similar to acne but are a major clue to a potentially lethal disease. Other manifestations of systemic candidiasis may include osteomyelitis, arthritis, meningitis, and abscesses in the brain, heart, liver, spleen and thyroid. Involvement of the lungs is also common, but pulmonary lesions are usually too small to be seen on chest X-ray. Finally, *Candida* endocarditis can occur in patients receiving prolonged intravenous therapy or cardiac valve implants, or in intravenous drug abusers. Fungal lesions appear on the valves, and can embolize and occlude large blood vessels.

Superficial infections are diagnosed by microscopic examination of scrapings or swabs of infected lesions in the presence of 10% potassium hydroxide. *Candida* organisms can also be seen on gram stain. Endocarditis is diagnosed by blood cultures or demonstration of bulky valvular lesions on echocardiography. Systemic candidiasis may be difficult to diagnose because the presence of heavy colonization at the usual sites of infection indicates, but does not prove, that dissemination has occurred. The most reliable evidence of systemic candidiasis is biopsy demonstration of tissue invasion or recovery of yeast from fluid in a closed body cavity, such as cerebral spinal fluid, pleural or peritoneal fluid. Similarly, positive blood or urine or sputum cultures may indicate invasive disease or simply localized disease around indwelling devices, *e.g.*, catheters or intravenous lines.

Mucocutaneous infections may be treated with topical preparations of nystatin, amphotericin B, clotrimazole, miconazole, haloprogin or gentian violet. Oropharyngeal or esophageal candidiasis can be treated with systemic

agents such as ketoconazole or fluconazole. Chronic mucocutaneous candidiasis syndrome may respond to topical or systemic therapeutic agents such as amphotericin B or ketoconazole, but often relapses when medication is discontinued. Cystitis may be treated with amphotericin B bladder rinses, or a brief low-dose intravenous course of amphotericin B with or without oral flucytosine. Endocarditis is essentially incurable without valve replacement, accompanied by a 6 to 10 week course of amphotericin B and flucytosine. Even with therapy, however, complete cure of endocarditis is not always possible.

The mortality rate from systemic candidiasis is about 50%. Systemic candidiasis may be treated with fluconazole, a fungistatic agent, or amphotericin B, a fungicidal agent although systemic use of the latter is limited by its toxicity. Both drugs have substantial adverse reactions when used in combination with cyclosporine A, which itself can be nephrotoxic. The removal of precipitating factors such as intravenous lines or catheters is also important for controlling infection. Flucytosine therapy can be added to the amphotericin B therapy for treatment of systemic candidiasis, especially in patients that are not immunocompromised. In immunocompromised patients, however, these infections are problematic and resist effective treatment. Mortality with systemic candidiasis can be over 90% in such patients. Furthermore, chronic mucocutaneous candidiasis and candidal endocarditis often show evidence of disease after having been declared cured.

There continues to exist a need in the art for new anti-fungal methods and materials. In particular, effective anti-fungal therapy for systemic mycoses is limited. Products and methods responsive to this need would ideally involve substantially non-toxic compounds available in large quantities by means of synthetic or recombinant methods. Ideal compounds would have a rapid effect and a broad spectrum of fungicidal or fungistatic activity against a variety of different fungal species when administered or applied as the sole anti-fungal agent. Ideal compounds would also be useful in combinative therapies with other anti-fungal agents, particularly where these activities would reduce the amount of

anti-fungal agent required for therapeutic effectiveness, enhance the effect of such agents, or limit potential toxic responses and high cost of treatment.

SUMMARY OF THE INVENTION

The present invention provides methods of treating a subject suffering from a fungal infection by administering a therapeutically effective amount of a BPI protein product. This is based on the surprising discovery that BPI protein products have fungicidal/fungistatic effects. BPI protein products may be administered alone or in conjunction with known anti-fungal agents. When made the subject of adjunctive therapy, the administration of BPI protein products may reduce the amount of anti-fungal agent needed for effective therapy, thus limiting potential toxic response and/or high cost of treatment. Administration of BPI protein products may also enhance the effect of such agents, accelerate the effect of such agents, or reverse resistance of fungi to such agents.

In addition, the invention provides a method of killing or inhibiting growth of fungi comprising contacting the fungi with a BPI protein product. This method can be practiced *in vivo* or in a variety of *in vitro* uses such as use to decontaminate fluids and surfaces and to sterilize surgical and other medical equipment and implantable devices, including prosthetic joints and indwelling invasive devices.

A further aspect of the invention involves use of a BPI protein product for the manufacture of a medicament for treatment of fungal infection. The medicament may include, in addition to a BPI protein product, other chemotherapeutic agents such as anti-fungal agents.

Numerous additional aspects and advantages of the invention will become apparent to those skilled in the art upon considering the following detailed description of the invention, which describes the presently preferred embodiments thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides results of broth assay tests of the activity of various BPI protein products against *C. albicans*.

Figures 2 and 3 graphically represent survival data in mice after *C. albicans* challenge and treatment with BPI-derived peptides or buffer.

Figure 4 graphically represents respiration rate in rats after *C. albicans* infection and treatment with $rBPI_{23}$ or thaumatin.

Figure 5 graphically represents arterial blood pressure in rats after *C. albicans* infection and treatment with $rBPI_{23}$ or thaumatin.

Figure 6 graphically represents the number of circulating *C. albicans* colony forming units in rats after infection and treatment with $rBPI_{23}$ or thaumatin.

Figure 7 graphically represents arterial pH in rats after *C. albicans* infection and treatment with $rBPI_{23}$ or thaumatin.

Figure 8 graphically represents arterial PO_2 in rats after *C. albicans* infection and treatment with $rBPI_{23}$ or thaumatin.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the surprising discovery that a BPI protein product can be administered to treat subjects suffering from fungal infection, and provides methods of treating such infections. Unexpectedly, BPI protein products were demonstrated to have anti-fungal activities both in *in vitro* killing assays and in *in vivo* models of fungal infection, as measured, for example, by improved survival or reduction of colony-forming units in circulation after fungal challenge. A variety of fungal infections, including infections caused by *Aspergillosis*, infections caused by *Cryptococcus*, such as cryptococcal meningitis, and mucocutaneous and systemic candidiasis caused by *Candida* species, may be treated according to the invention.

The BPI protein product may be administered systemically or topically. Systemic routes of administration include oral, intravenous,

.intramuscular or subcutaneous injection (including into depots for long-term release), intraocular or retrobulbar, intrathecal, intraperitoneal (e.g. by intraperitoneal lavage), transpulmonary using aerosolized or nebulized drug, or transdermal. Topical routes include administration in the form of salves, ophthalmic drops, ear drops, or irrigation fluids (for, e.g., irrigation of wounds).

The BPI protein product may be administered in conjunction with other anti-fungal agents presently known to be effective. Preferred anti-fungal agents for this purpose are amphotericin B and fluconazole. Concurrent administration of BPI protein product with anti-fungal agents is expected to improve the therapeutic effectiveness of the anti-fungal agents. This may occur through reducing the concentration of anti-fungal agent required to eradicate or inhibit fungal growth, *e.g.*, replication. Because the use of some agents is limited by their systemic toxicity or prohibitive cost, lowering the concentration of anti-fungal agent required for therapeutic effectiveness reduces toxicity and/or cost of treatment, and thus allows wider use of the agent. Concurrent administration of BPI protein product and another anti-fungal agent may produce a more rapid or complete fungicidal/fungistatic effect than could be achieved with either agent alone. BPI protein product administration may reverse the resistance of fungi to anti-fungal agents. BPI protein product administration may also convert a fungistatic agent into a fungicidal agent.

An advantage provided by the present invention is the ability to treat fungal infections, particularly *Candida* infections, that are presently considered incurable. Another advantage is the ability to treat fungi that have acquired resistance to known anti-fungal agents. A further advantage of concurrent administration of BPI with an anti-fungal agent having undesirable side effects, *e.g.*, amphotericin B, is the ability to reduce the amount of anti-fungal agent needed for effective therapy. The present invention may also provide quality of life benefits due to, e.g., decreased duration of therapy, reduced stay in intensive care units or reduced stay overall in the hospital, with the concomitant reduced risk of serious nosocomial (hospital-acquired) infections.

"Concurrent administration" as used herein includes administration of the agents together, or before or after each other. The BPI protein products and anti-fungal agents may be administered by different routes. For example, the BPI protein product may be administered intravenously while the anti-fungal agents are administered intramuscularly, intravenously, subcutaneously, orally or intraperitoneally. Alternatively, the BPI protein product may be administered intraperitoneally while the anti-fungal agents are administered intraperitoneally or intravenously, or the BPI protein product may be administered in an aerosolized or nebulized form while the anti-fungal agents are administered, e.g., intravenously. The BPI protein product and anti-fungal agents may be both administered intravenously. The BPI protein product and anti-fungal agents may be given sequentially in the same intravenous line, after an intermediate flush, or may be given in different intravenous lines. The BPI protein product and anti-fungal agents may be administered simultaneously or sequentially, as long as they are given in a manner sufficient to allow both agents to achieve effective concentrations at the site of infection.

Concurrent administration of BPI protein product and antibiotic is expected to provide more effective treatment of fungal infections. Concurrent administration of the two agents may provide greater therapeutic effects *in vivo* than either agent provides when administered singly. For example, concurrent administration may permit a reduction in the dosage of one or both agents with achievement of a similar therapeutic effect. Alternatively, the concurrent administration may produce a more rapid or complete fungicidal/fungistatic effect than could be achieved with either agent alone.

Therapeutic effectiveness is based on a successful clinical outcome, and does not require that the anti-fungal agent or agents kill 100% of the organisms involved in the infection. Success depends on achieving a level of anti-fungal activity at the site of infection that is sufficient to inhibit the fungi in a manner that tips the balance in favor of the host. When host defenses are maximally effective, the anti-fungal effect required may be minimal. Reducing organism load by even one log (a factor of 10) may permit the host's own

defenses to control the infection. In addition, augmenting an early fungicidal/fungistatic effect can be more important than long-term fungicidal/fungistatic effect. These early events are a significant and critical part of therapeutic success, because they allow time for host defense mechanisms to activate.

BPI protein product is thought to interact with a variety of host defense elements present in whole blood or serum, including complement, p15 and LBP, and other cells and components of the immune system. Such interactions may result in potentiation of the activities of BPI protein product. Because of these interactions, BPI protein products can be expected to exert even greater activity *in vivo* than *in vitro*. Thus, while *in vitro* tests are predictive of *in vivo* utility, absence of activity *in vitro* does not necessarily indicate absence of activity *in vivo*. For example, BPI has been observed to display a greater bactericidal effect on gram-negative bacteria in whole blood or plasma assays than in assays using conventional media. [Weiss et al., *J. Clin. Invest. 90*:1122-1130 (1992)]. This may be because conventional *in vitro* systems lack the blood elements that facilitate or potentiate BPI's function *in vivo*, or because conventional media contain higher than physiological concentrations of magnesium and calcium, which are typically inhibitors of the activity of BPI protein products. Furthermore, in the host, BPI protein product is available to neutralize translocation of gram-negative bacteria and concomitant release of endotoxin, a further clinical benefit not seen in or predicted by *in vitro* tests of anti-fungal activity.

It is also contemplated that the BPI protein product be administered with other products that potentiate the activity of BPI protein products, including the anti-fungal activity of BPI protein products. For example, serum complement potentiates the gram-negative bactericidal activity of BPI protein products; the combination of BPI protein product and serum complement provides synergistic bactericidal/growth inhibitory effects. See, e.g., Ooi *et al. J. Biol. Chem., 265*: 15956 (1990) and Levy *et al. J. Biol. Chem., 268*: 6038-6083 (1993) which address naturally-occurring 15 kD proteins potentiating BPI antibacterial activity.

See also co-owned, co-pending PCT Application No. US94/07834 filed July 13, 1994, which corresponds to U.S. Patent Application Serial No. 08/274,303 filed July 11, 1994 as a continuation-in-part of U.S. Patent Application Serial No. 08/093,201 filed July 14, 1993. These applications, which are all incorporated herein by reference, describe methods for potentiating gram-negative bactericidal activity of BPI protein products by administering lipopolysaccharide binding protein (LBP) and LBP protein products. LBP protein derivatives and derivative hybrids which lack CD-14 immunostimulatory properties are described in PCT Application No. US94/06931 filed June 17, 1994, which corresponds to co-owned, co-pending U.S. Patent Application Serial No. 08/261,660, filed June 17, 1994 as a continuation-in-part of U.S. Patent Application Serial No. 08/079,510, filed June 17, 1993, the disclosures of all of which are hereby incorporated by reference. It has also been observed that poloxamer surfactants enhance the anti-bacterial activity of BPI protein products, as described in Lambert, U.S. Application No. _____ filed January 13, 1995 [Attorney Docket No. 27129/32424]; poloxamer surfactants may also enhance the activity of anti-fungal agents.

Without being bound by a theory of the invention, it is believed that BPI protein products may have several modes of action. BPI protein product, through its heparin-binding ability, may interfere with the binding of fungi to the extracellular matrix. For example, heparin-like surface molecules of *Candida* are believed to mediate adhesion of the yeast to extracellular matrix and host tissues. BPI protein product may also act directly on the cytoplasmic membrane of fungi. In addition, BPI may bind to fungal cell wall mannoproteins that are structurally similar to the LPS of gram-negative organisms or that are responsible for adherence to target host tissues, thus interfering with fungal interaction with host tissues. Binding to fungal mannans may also promote access of BPI protein product to the inner cytoplasmic membrane. Finally, because fungal infection may cause stress-induced translocation of bowel flora and/or LPS, BPI may also act beneficially by killing gram-negative bacteria and neutralizing LPS.

In addition, the invention provides a method of killing or inhibiting growth of fungi comprising contacting the fungi with a BPI protein product. This method can be practiced *in vivo* or in a variety of *in vitro* uses such as use in food preparations or to decontaminate fluids and surfaces or to sterilize surgical and other medical equipment and implantable devices, including prosthetic joints. These methods can also be used for *in situ* sterilization of indwelling invasive devices such as intravenous lines and catheters, which are often foci of infection.

A further aspect of the invention involves use of a BPI protein product for the manufacture of a medicament for treatment of fungal infection. The medicament may include, in addition to a BPI protein product, other chemotherapeutic agents such as anti-fungal agents. The medicament can optionally comprise a pharmaceutically acceptable diluent, adjuvant or carrier.

As used herein, "BPI protein product" includes naturally and recombinantly produced BPI protein; natural, synthetic, and recombinant biologically active polypeptide fragments of BPI protein; biologically active polypeptide variants of BPI protein or fragments thereof, including hybrid fusion proteins and dimers; biologically active polypeptide analogs of BPI protein or fragments or variants thereof, including cysteine-substituted analogs; and BPI-derived peptides. The BPI protein products administered according to this invention may be generated and/or isolated by any means known in the art. U.S. Patent No. 5,198,541, the disclosure of which is incorporated herein by reference, discloses recombinant genes encoding, and methods for expression of, BPI proteins including recombinant BPI holoprotein, referred to as $rBPI_{50}$ and recombinant fragments of BPI. Co-owned, copending U.S. Patent Application Ser. No. 07/885,501 and a continuation-in-part thereof, U.S. Patent Application Ser. No. 08/072,063 filed May 19, 1993 and corresponding PCT Application No. 93/04752 filed May 19, 1993, which are all incorporated herein by reference, disclose novel methods for the purification of recombinant BPI protein products expressed in and secreted from genetically transformed mammalian host cells in culture and discloses how one may produce large quantities of recombinant BPI

products suitable for incorporation into stable, homogeneous pharmaceutical preparations.

Biologically active fragments of BPI (BPI fragments) include biologically active molecules that have the same or similar amino acid sequence as a natural human BPI holoprotein, except that the fragment molecule lacks amino-terminal amino acids, internal amino acids, and/or carboxy-terminal amino acids of the holoprotein. Nonlimiting examples of such fragments include a N-terminal fragment of natural human BPI of approximately 25 kD, described in Ooi et al., *J. Exp. Med.*, *174*:649 (1991), and the recombinant expression product of DNA encoding N-terminal amino acids from 1 to about 193 to 199 of natural human BPI, described in Gazzano-Santoro et al., *Infect. Immun.* *60*:4754-4761 (1992), and referred to as $rBPI_{23}$. In that publication, an expression vector was used as a source of DNA encoding a recombinant expression product ($rBPI_{23}$) having the 31-residue signal sequence and the first 199 amino acids of the N-terminus of the mature human BPI, as set out in Figure 1 of Gray et al., *supra*, except that valine at position 151 is specified by GTG rather than GTC and residue 185 is glutamic acid (specified by GAG) rather than lysine (specified by AAG). Recombinant holoprotein (rBPI) has also been produced having the sequence (SEQ ID NOS: 145 and 146) set out in Figure 1 of Gray et al., *supra*, with the exceptions noted for $rBPI_{23}$ and with the exception that residue 417 is alanine (specified by GCT) rather than valine (specified by GTT). Other examples include dimeric forms of BPI fragments, as described in co-owned and co-pending U.S. Patent Application Serial No. 08/212,132, filed March 11, 1994, and corresponding PCT Application No. _____, the disclosures of which are incorporated herein by reference. Preferred dimeric products include dimeric BPI protein products wherein the monomers are amino-terminal BPI fragments having the N-terminal residues from about 1 to 175 to about 1 to 199 of BPI holoprotein. A particularly preferred dimeric product is the dimeric form of the BPI fragment having N-terminal residues 1 through 193, designated $rBPI_{42}$ dimer.

Biologically active variants of BPI (BPI variants) include but are not limited to recombinant hybrid fusion proteins, comprising BPI holoprotein or biologically active fragment thereof and at least a portion of at least one other polypeptide, and dimeric forms of BPI variants. Examples of such hybrid fusion proteins and dimeric forms are described by Theofan et al. in co-owned, copending U.S. Patent Application Serial No. 07/885,911, and a continuation-in-part application thereof, U.S. Patent Application Serial No. 08/064,693 filed May 19, 1993 and corresponding PCT Application No. US93/04754 filed May 19, 1993, which are all incorporated herein by reference and include hybrid fusion proteins comprising, at the amino-terminal end, a BPI protein or a biologically active fragment thereof and, at the carboxy-terminal end, at least one constant domain of an immunoglobulin heavy chain or allelic variant thereof.

Biologically active analogs of BPI (BPI analogs) include but are not limited to BPI protein products wherein one or more amino acid residues have been replaced by a different amino acid. For example, co-owned, copending U.S. Patent Application Ser. No. 08/013,801 filed February 2, 1993 and corresponding PCT Application No. US94/01235 filed February 2, 1994, the disclosures of which are incorporated herein by reference, discloses polypeptide analogs of BPI and BPI fragments wherein a cysteine residue is replaced by a different amino acid. A stable BPI protein product described by this application is the expression product of DNA encoding from amino acid 1 to approximately 193 or 199 of the N-terminal amino acids of BPI holoprotein, but wherein the cysteine at residue number 132 is substituted with alanine and is designated $rBPI_{21}\Delta cys$ or $rBPI_{21}$. Other examples include dimeric forms of BPI analogs; e.g. co-owned and co-pending U.S. Patent Application Serial No. 08/212,132 filed March 11, 1994, and corresponding PCT Application No. _____, the disclosures of which are incorporated herein by reference.

Other BPI protein products useful according to the methods of the invention are peptides derived from or based on BPI produced by recombinant or synthetic means (BPI-derived peptides), such as those described in co-owned and copending PCT Application No. US94/10427 filed September 15, 1994, which

corresponds to U.S. Patent Application Serial No. 08/306,473, filed September 15, 1994, and PCT Application No. US94/02465 filed March 11, 1994, which corresponds to U.S. Patent Application Serial No. 08/209,762, filed March 11, 1994, which is a continuation-in-part of U.S. Patent Application Serial No. 08/183,222, filed January 14, 1994, which is a continuation-in-part of U.S. Patent Application Ser. No. 08/093,202 filed July 15, 1993 (for which the corresponding international application is PCT Application No. US94/02401 filed March 11, 1994), which is a continuation-in-part of U.S. Patent Application Ser. No. 08/030,644 filed March 12, 1993, the disclosures of all of which are incorporated herein by reference.

Presently preferred BPI protein products include recombinantly-produced N-terminal fragments of BPI, especially those having a molecular weight of approximately between 21 to 25 kD such as $rBPI_{23}$ or $rBPI_{21}$, or dimeric forms of these N-terminal fragments (e.g., $rBPI_{42}$ dimer). Additionally, preferred BPI protein products include $rBPI_{50}$ and BPI-derived peptides. Presently preferred BPI-derived peptides include those having an amino acid sequence of BPI protein from about position 142 to about position 169, subsequences thereof and variants of the sequence or subsequence thereof, which possess a BPI anti-fungal biological activity.

The administration of BPI protein products is preferably accomplished with a pharmaceutical composition comprising a BPI protein product and a pharmaceutically acceptable diluent, adjuvant, or carrier. The BPI protein product may be administered without or in conjunction with known surfactants, other chemotherapeutic agents or additional known anti-fungal agents. A stable pharmaceutical composition containing BPI protein products (e.g., $rBPI_{50}$, $rBPI_{23}$) comprises the BPI protein product at a concentration of 1 mg/ml in citrate buffered saline (5 or 20 mM citrate, 150 mM NaCl, pH 5.0) comprising 0.1% by weight of poloxamer 188 (Pluronic F-68, BASF Wyandotte, Parsippany, NJ) and 0.002% by weight of polysorbate 80 (Tween 80, ICI Americas Inc., Wilmington, DE). Another stable pharmaceutical composition containing BPI protein products (e.g., $rBPI_{21}$) comprises the BPI protein product

at a concentration of 2 mg/ml in 5 mM citrate, 150 mM NaCl, 0.2% poloxamer 188 and 0.002% polysorbate 80. Such preferred combinations are described in co-owned, co-pending PCT Application No. US94/01239 filed February 2, 1994, which corresponds to U.S. Patent Application Ser. No. 08/190,869 filed February 2, 1994 and U.S. Patent Application Ser. No. 08/012,360 filed February 2, 1993, the disclosures of all of which are incorporated herein by reference.

Other aspects and advantages of the present invention will be understood upon consideration of the following illustrative examples wherein Example 1 addresses preparation and *in vitro* anti-fungal testing of BPI protein products; Example 2 addresses the *in vivo* effect of BPI protein products on survival rate of mice challenged with *Candida*; Example 3 addresses additional *in vitro* and *in vivo* testing of the anti-fungal effect of BPI protein products on a variety of fungal species; Example 4 addresses the *in vivo* anti-fungal effect of BPI protein products in rats; and Example 5 addresses further *in vivo* testing of anti-fungal effects.

Example 1

IN VITRO ANTI-FUNGAL EFFECTS

This example addresses *in vitro* screening of BPI protein products, and specifically BPI-derived peptides, for anti-fungal activity in a broth assay and/or in a radial diffusion assay.

The BPI-derived peptides tested were all prepared according to the procedures described in parent U.S. Patent Application Serial Nos. 08/209,762 and 08/183,222. Briefly summarized, peptides were prepared by solid phase peptide synthesis according to the methods of Merrifield, *J. Am Chem. Soc. 85*: 2149 (1963) and Merrifield *et al. Anal. Chem., 38*: 1905-1914 (1966) using an Applied Biosystems, Inc. Model 432 peptide synthesizer. Alternatively, peptides may be synthesized by the procedure described in Example 2, *infra*. Peptide design was based in part on the discovery of three functional domains present in the NH_2-terminal region of the BPI holoprotein: domain I comprising BPI amino acids from about position 17 to about position 45 (SEQ ID NO: 1); domain II

comprising BPI amino acids from about position 65 to about 99 (SEQ ID NO: 6); and domain III comprising BPI amino acids from about position 142 to about position 169 (SEQ ID NO: 12). Peptides include sequences and subsequences of the domain sequences and variants thereof, including linear and branched chain combination peptides with and without single or multiple amino acid (including atypical amino acid) substitutions as well as cyclized peptides and interdomain sequence peptides. Table 1 below sets out peptides derived from or based on BPI sequences, which are identified by peptide number with a prefix XMP or BPI (e.g., XMP.1 or BPI.1, XMP.2 or BPI.2, etc.), SEQ ID NO:, amino acid sequence based on reference to position within BPI and designation of amino acid substitutions and additions. Also set out in Table 1 are mass spectroscopy and HPLC estimates of purity of the peptides.

In each broth assay screening procedure, a colony of *C. albicans* designated CA-1, Strain SLU #1 that was received from the laboratories of G. Manischak and A. Lechner, St. Louis University Hospital, St. Louis, MO, where the strain was maintained, was inoculated into a tube containing 5 ml Sabouraud Dextrose broth (2% dextrose, 1% neopeptone) and incubated overnight at 37°C with shaking. The overnight culture was diluted 1:50 into 5 ml of fresh broth and incubated for 3 hours at 37°C. Organisms were pelleted by centrifugation in a Beckman J-6M centrifuge for 5 minutes at 3000 rpm (1500 x g) and the pellets were resuspended in 5 ml phosphate buffered saline (PBS) and the optical density at 570 nm was determined. On the basis of the determination that one OD unit equals 3 x 10^7 colony forming units/ml, yeast cells were diluted to 2 x 10^6 cells/ml in Sabouraud Dextrose broth.

Peptides derived from or based on BPI to be screened were originally constituted in Dulbecco's-PBS, were diluted to 100 μg/ml in broth and were serially diluted 2-fold into wells of a 96 well sterile, flat bottom, non-pyrogenic tissue culture plate (Costar, Cambridge, MA). All assays were performed in triplicate. 2 x 10^5 organisms were added at 100 μl per well; the plate was incubated on a shaker at 37°C for 18 hours; and the optical densities for each well were read at 590 nm. Figure 1 hereto graphically illustrates the

dose response curves for five peptides (XMP.13, XMP.138, XMP.139, XMP.142 and XMP.143). All illustrated peptides reduced optical density of the cultures to below 0.1 at doses of less than about 50 μg/ml, with XMP.138 displaying the best results of the illustrated peptides at low dosages. Table 1 sets out broth assay data in terms of minimum inhibitory concentration (MIC), i.e. the lowest concentration required to reduce the optical density at 590 nm to below 0.1.

In the radial diffusion assay procedures, yeast CA-1 cultures and peptide solutions were prepared as in the broth assay procedure described above. Ten mL of molten underlayer agarose comprising 3% Sabouraud Dextrose broth, 1% agarose (Pharmacia, Piscataway, NJ), 0.02% Tween 20, and 10 mM sodium phosphate, at pH 7.4 was added to polystyrene tubes and maintained in a 56°C water bath until the addition of yeast. Tubes were cooled to approximately 45°C, yeast were added to give a final concentration of 1 x 10^6 CFU/ml, and the tubes were mixed again by inverting. The contents were poured into level square petri dishes and distributed evenly. The agarose solidified in less than 30 seconds and had a uniform thickness of about 1 mm. A series of wells were punched into the hardened agarose using a sterile 3 mm punch attached to a vacuum apparatus.

Peptides to be assayed were 2-fold serially diluted in Dulbecco's PBS (D-PBS) starting from a concentration of approximately 1 mg/mL. Five μL of each dilution was added to each well and the plates were incubated at 37°C for 3 hours. An overlayer of 10 mL of molten agarose comprising 6% Sabouraud Dextrose broth, 1% agarose, and 10 mM sodium phosphate, pH 7.4, (at approximately 45°C) was then added and plates were incubated overnight at 37°C. Following this overnight incubation, a dilute Coomassie solution was poured into the plates and allowed to stain for 24 hours.

Clear zones of growth inhibition around each well were measured with calipers. The actual area of growth inhibition (mm^2) was calculated by subtracting the area of the well. Table 1 below sets out the results of the radial diffusion assays for tested peptides in terms of the number of picomoles (pmol) of peptide required to establish a 30 mm^2 area of growth inhibition.

Peptides XMP.221 through XMP.281 (SEQ ID NOS: 166 through 226) are prepared and tested for anti-fungal activity as described above.

Further experiments are performed to determine the anti-fungal activity of BPI protein products on strains of *Candida* considered resistant to other anti-fungal agents: polyene-resistant *C. albicans* (ATCC Accession No. 38247), 5-fluorocytosine-resistant *C. albicans* (ATCC No. 44373), azole-resistant *C. albicans* (ATCC No. 62342), and ketoconazole-resistant *C. albicans* (ATCC No. 64124).

TABLE 1

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm^2 zone
XMP.1 (4)	19-33	-	2 Peaks	x	x
XMP.2 (7)	85-99	64	37.2	>50	x
XMP.3 (11)	73-99	-	17	x	x
XMP.4 (3)	25-46	-	No Peak	x	x
XMP.5 (67)	142-163	-	18	x	x
XMP.7 (54)	(90-99) x 2	69	27	50.00	x
XMP.8 (8)	90-99	79	Mixture	>100.00	x
XMP.9 (51)	95-99,90-99	-	29	x	x
XMP.10 (55, 65)	94-99, 90-99, 90-99 and 95-99, 90-99, 90-99	-	Mixture	x	x
XMP.11 (13)	148-151,153-161	-	76	x	x
XMP.12 (14)	141-169	-	26	>100.00	x
XMP.13 (15)	148-161	78	69	12.5	222
XMP.13P (15)	148-161	100	98	6.25	x

TABLE 1 (continued)

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm² zone
XMP.14 (2)	21-50	-	-	x	x
XMP.15 (16)	85-99, A @ 85 (I)	66	57.6	x	x
XMP.16 (17)	85-99, A @ 86 (K)	-	84.1	x	x
XMP.17 (18)	85-99, A @ 87 (I)	86	77,67	x	x
XMP.18 (19)	85-99, A @ 88 (S)	66	70	x	x
XMP.19 (20)	85-99, A @ 89 (G)	-	69	x	x
XMP.20 (21)	85-99, A @ 90 (K)	-	66	x	x
XMP.21 (22)	85-99, A @ 91 (W)	68	65.8	x	x
XMP.22 (23)	85-99, A @ 92 (K)	-	66	x	x
XMP.23 (24)	85-99, A @ 94 (Q)	-	69	x	x
XMP.24 (25)	85-99, A @ 95 (K)	-	67	x	x
XMP.25 (26)	85-99, A @ 96 (R)	-	73	x	x
XMP.26 (27)	85-99, A @ 97 (F)	-	73	x	x
XMP.27 (28)	85-99, A @ 98 (L)	-	65	x	x

TABLE 1 (continued)

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm^2 zone
XMP.28 (29)	85-99, A @ 99 (K)	-	80	x	x
XMP.29 (56)	(148-161) x 2	-	26	>50	>1469
XMP.30 (52)	90-99,148-161	-	21	x	>1653
XMP.30-P (52)	90-99,148-161	95	98	>50	1663
XMP.31 (33)	148-161, A @ 148 (K)	-	68	6.25	426
XMP.32 (34)	148-161, A @ 149 (S)	-	70	3.13	294
XMP.33 (35)	148-161, A @ 150 (K)	-	58	6.25	603
XMP.34 (36)	148-161, A @ 151 (V)	-	51	6.25	319
XMP.35 (37)	148-161, A @ 152 (G)	-	72	3.13	442
XMP.36 (38)	148-161, A @ 153 (W)	-	64	6.25	197
XMP.37 (39)	148-161, A @ 154 (L)	-	51	6.25	253
XMP.38 (40)	148-161, A @ 155 (I)	-	70	6.25	391
XMP.39 (41)	148-161, A @ 156 (Q)	-	53	12.50	1792
XMP.40 (42)	148-161, A @ 157 (L)	-	53	3.13	253

TABLE 1 (continued)

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm² zone
XMP.41 (43)	148-161, A @ 158 (F)	-	63	3.13	734
XMP.42 (44)	148-161, A @ 159 (H)	-	59	6.25	549
XMP.43 (45)	148-161, A @ 160 (K)	-	53	12.50	785
XMP.44 (46)	148-161, A @ 161 (K)	-	70	6.25	578
XMP.45 (31)	85-99, A @ 94(Q)&95(K)	71	46	x	x
XMP.46 (57)	(90-99)x2, A @ 1st 94(Q)&95(K)	67	47	x	x
XMP.47 (58)	(90-99)x2, A @ 2d 94(Q)&95(K)	57	34	x	x
XMP.48 (59)	(90-99)x2, A @ both 94(Q)&95(K)	68	33	>50	x
XMP.54 (5)	21-35	-	-	x	x
XMP.55 (61)	152-172	-	28	x	x
XMP.56 (47)	85-99, K @ 94 (Q) & Q @ 95(K)	-	55	x	x
XMP.57 (99)	Cys 85-99 Cys	50	Mixture	x	x

TABLE 1 (continued)

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm^2 zone
XMP.58 (9)	Cys-85-99	49	25.7	x	x
XMP.59 (30)	85-99, A @ 90(K)&92(K)	56	30.3	x	x
XMP.60 (32)	85-99, A @ 86(K)&99(K)	57	78.3	x	x
XMP.61 (48)	85-99, F @ 91(W)	60	59.8	x	x
XMP.63 (53)	85-99, 148-161	38	31.3	x	>1006
XMP.65 Rd (68)	Cys-85-99-Cys	41	22, 34	x	x
XMP.65 Ox (10)	Cys-85-99-Cys	-	No Peak	x	x
XMP.66 (49)	85-99, W_D @ 91(W)	-	70	x	x
XMP.67 (50)	85-99, β-(1-naphthyl)-A @ 91	65	52	x	x
XMP.69 (60)	[90-99, A @ 94 (Q) & 95 (K)] x 3	44	54, 40	x	x
XMP.70 (63)	85-99, β-(3-pyridyl)-A @ 91	66	54	x	x
XMP.71 (64)	A_D-A_D-85-99	-	60	x	x

TABLE 1 (continued)

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm² zone
XMP.72 (66)	85-99, β-(3-pyridyl)-A @ 97 (F)	-	52	x	x
XMP.73 (62)	85-99, F @ 95 (K)	-	44, 39	x	x
XMP.74 (70)	148-161, 90-99	-	29	x	>2148
XMP.75 (100)	IKKRAISFLGKKWQK (2-mixed)	-	32	x	x
XMP.76 (71)	85-99, F_D @ 95 (K)	53	39	x	x
XMP.77 (72)	85-99, W @ 95 (K)	-	38	x	x
XMP.79 (73)	85-99, K @ 94 (Q)	-	48	x	x
XMP.80 (74)	85-99, β-(1-naphthyl)-A @ 95 (K)	71	44	x	x
XMP.81 (75)	85-99, F @ 94 (Q)	44	33, 35	x	x
XMP.82 (76)	148-161, W @ 158 (F)	82	58	3.13	518
XMP.83 (77)	148-161, β(1-naphthyl)-A @ 153 (W)	85	63	x	1804

TABLE 1 (continued)

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm² zone
XMP.84 (78)	85-99, β-(1-naphthyl) A @ 91 (W) & F @ 95 (K)	64	50	x	x
XMP.85 (79)	148-161, L @ 152 (G)	79	74	x	>1881
XMP.86 (80)	148-161, L @ 156 (Q)	69	51	x	>2048
XMP.87 (81)	148-161, L @ 159 (H)	79	63	x	>1536
XMP.88 (82)	85-99, F @ 94 (Q) & 95 (K)	62	50	x	x
XMP.89 (84)	85-99, β-(1-naphthyl) A @ 91 (W) & F @ 94 (Q)	66	50	x	x
XMP.90 (85)	85-99, β-(1-naphthyl) A @ 91 (W), F @ 94 (Q) & 95 (K)	70	63	x	x
XMP.91 (86)	148-161, F @ 156 (Q)	-	31	x	>3844
XMP.92 (87)	148-161, K @ 156 (Q)	-	50	3.13	299
XMP.93 (88)	85-99 148-161 β-(1-naphthyl) A @ 91 (W), F @ 95 (K)	72	38	x	>980

TABLE 1 (continued)

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm² zone
XMP.94 (89)	148-161, F @ 159 (H)	-	59	x	>923
XMP.95 (90)	148-161, F @ 152 (G)	-	57	x	>1398
XMP.96 (101)	148-161, F @ 161 (K)	-	60	x	1856
XMP.97 (92)	148-161, K @ 152 (G)	-	67	3.13	213
XMP.98 (83)	90-99, β-(1-naphthyl) A @ 91 (W), F @ 95 (K) + 148-161 F @ 156(Q)	69	31	x	x
XMP.99 (93)	[90-99, W @ 95 (K)]x3	-	-	x	x
XMP.100 (94)	148-161, K @ 152 (G) & 156 (Q)	-	61	6.25	462
XMP.101 (95)	(148-161) x 2[K @ 152(G) & 156(Q), F @ 159(H) & 161(K)]	-	16	x	x
XMP.102 (96)	90-99 (F @ 95(K)) + 148-161 L @ 156(Q)	-	16	x	x

TABLE 1 (continued)

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm² zone
XMP.103 (102)	85-99, W @ 94 (Q)	-	28	x	1151
XMP.104 (103)	148 - 161, S @ 156 (Q)	-	34	x	>5569
XMP.105 (104)	85-99, β-(1-naphthyl)-A @ 94 (Q)	58	43	x	1565
XMP.106 (105)	148 - 161, T @ 156 (Q)	-	26	x	1032
XMP.107 (106)	148 - 161, W @ 159 (H)	-	55	x	>2796
XMP.108 (107)	148 - 161, W @ 161 (K)	-	50	x	>3219
XMP.109 (108)	148-161, β(1-naphthyl) - A @ 158 (F)	-	41	x	x
XMP.110 (109)	148-161, β(1-naphthyl) - A @ 159 (H)	-	56	x	x
XMP.111 (110)	148-161, β(1-naphthyl) - A @ 161 (K)	-	73	x	x
XMP.112 (111)	85-99, β(1-naphthyl)A @ 91 (W) & 95 (K)	-	56	x	x
XMP.113 (112)	148 - 161, F @ 157 (L)	-	46	x	x

TABLE 1 (continued)

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm^2 zone
XMP.114 (113)	KWQLRSKGKIKIFKA	-	17	x	x
XMP.116 (114)	148-161, K @ 152 (G), β(1-naphthyl)A @ 153 (W)	-	72	x	670
XMP.119 (115)	85-99, β(1-naphthyl)A @ 91 (W) & 94 (K)	-	77	x	x
XMP.120 (116)	85 - 99, K @ 97 (F)	-	52	x	x
XMP.121 (117)	85-99, β(1-naphthyl)A @ 94 (Q) & 95 (K)	65	35	x	x
XMP.122 (118)	85-99, β(1-naphthyl)A @ 91 (W), 94(Q) & 95 (K)	-	46	x	x
XMP.123 (119)	148-161, p-Amino-F @ 156 (Q)	-	64	12.50	1721
XMP.124 (120)	148-161, K @ 152(G), W @ 158 (F)	–	67	6.25	351
XMP.125 (121)	148 - 161, Y @ 156 (Q)	-	54	25.00	>3150
XMP.126 (122)	148 - 161, W_D @ 153 (W)	66	54	25.00	1404

TABLE 1 (continued)

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm² zone
XMP.127 (123)	148 - 161, F @ 153 (W)	65	63	3.13	226
XMP.128 (124)	148 - 161 F_D @ 153 (W)	63	51	25.00	1179
XMP.129 (125)	148-161, 1-β(1-naphthyl)A_D @ 153 (W)	24	28	25.00	2117
XMP.130 (126)	148-161, 2-β(1-naphthyl)A @ 153 (W)	55	80	50.00	1159
XMP.131 (127)	148-161, 2-β(1-naphthyl)A_D @ 153 (W)	75	60	50.00	2493
XMP.132 (128)	148 - 161, Pyr-A @ 153 (W)	49	50	12.50	353
XMP.133 (129)	148-161, p-Amino-F @ 153 (W)	63	47	12.50	284
XMP.134 (130)	148-161, p-Amino-F @ 152 (G)	-	68	12.50	1255
XMP.135 (131)	148 - 161, K @ 153 (W)	-	70	6.25	428
XMP.136 (132)	85 - 99, E @ 95 (K)	-	50	x	x
XMP.137 (133)	Cys-148-161-Cys	-	28	x	>2286

TABLE 1 (continued)

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm² zone
XMP.138 (134)	148-161, K @ 152 (G), F @ 153 (W)	-	61	3.13	257
XMP.139 (135)	148-161, Y @ 153 (W)	-	60	6.25	323
XMP.140 (136)	90-99 β(1-naphthyl)A @ 94 (Q) & 95 (K) + 104	-	26	x	x
XMP.141 (137)	85 - 99, W @ 97 (F)	-	50	x	x
XMP.142 (138)	148 - 161, W @ 157 (L)	-	57	12.50	1244
XMP.143 (139)	148-161, β(1-naphthyl)A @ 157 (L)	-	65	25.00	>2839
XMP.144 (140)	148-161, Cyclohexyl-A @ 153 (W)	-	60	12.50	695
XMP.145 (141)	90-99, β(1-naphthyl)A @ 94(Q) & 95(K) + 148-161	-	20	x	>1887
XMP.146 (142)	148-161, β(1-naphthyl)A @ 159(H) & 161(K)	-	53	>50.00	>2717
XMP.147 (143)	85 - 99 K @ 96 (R)	-	55	100	>2558

TABLE 1 (continued)

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm^2 zone
XMP.148 (144)	148-161, β(1-naphthyl)A @ 153 (W) & 159 (H)	-	62	50.00	>2805
XMP.149 (147)	KWKVFKKIEK + 148-161	-	27	12.50	>1,397
XMP.150 (148)	KWAFAKKQKKRLKRQWLKKF	-	Mixture	x	>2,380
XMP.151 (55)	94-99, 90-99, 90-99	-	14	x	x
XMP.152 (65)	95-99, 90-99, 90-99	-	21	x	x
XMP.153 (149)	(90-99) x 3	-	17	x	x
XMP.154 (150)	(90-99) x 2, β(1-naphthyl)A @ 1st 94 (Q) & 95 (K)	-	31	>100.00	x
XMP.155 (151)	(90-99) x 2, β(1-naphthyl)A @ 2nd 94 (Q) & 94 (K)	-	23	>100.00	x
XMP.156 (152)	(90-99) X 2, β(1-naphthyl)A @ both 94 (Q) & 95 (K)	-	38	>100.00	x
XMP.157 (153)	(90-99, β(1-naphthyl)A @ 94 (Q) & 95 (K)) x 3	-	38	>100.00	x

TABLE 1 (continued)

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm² zone
XMP.158 (154)	85-99, 148-161, β(1-naphthyl)A @ 94 (Q) & 95 (K)	-	16	>100.00	x
XMP.159 (155)	(90-99, β(1-naphthyl)A @ 91 (W) & 95 (K)) + 82	-	23	50.00	x
XMP.160 (156)	(90-99) x 2, β(1-naphthyl)A @ both 91 (W) & 95 (K)	-	32	>100.00	x
XMP.161 (157)	148-161, K @ 152 (G) & A @ 153 (W)	-	75	3.13	x
XMP.162 (158)	90-99, 148-161, W @ 95 (K)	-	21	x	x
XMP.163 (159)	(90-99) x 2, W @ both 95 (K)	-	Mixture	x	x
XMP.164 (160)	(90-99) x 2, β (1-naphthyl)A @ both 94 (Q)	-	46	x	x
XMP.165 (161)	(90-99, β (1-naphthyl)A @ 91 (W) & F @ 95 (K)) x 2	-	72	x	x
XMP.166 (162)	148-161, V @ 153 (W)	-	68	3.13	170.65
XMP.167 (163)	90-97	-	56	>50.00	x

TABLE 1 (continued)

Peptide # (Seq. ID No.)	Protein AA Segment	MS % Purity	HPLC % Purity	*C. albicans*	
				MIC (μg/ml)	pmol/ 30 mm^2 zone
XMP.168 (164)	C- 90-101-C	-	13	>100.00	x
XMP.169 (165)	C-90-97-C	-	20	>100.00	x
XMP.170 (227)	90-101	-	69	>50.00	x
x = Not tested					

Example 2

IN VIVO ANTI-FUNGAL EFFECT OF BPI PROTEIN PRODUCTS IN MICE WITH SYSTEMIC *CANDIDA* INFECTION

This example addresses the *in vivo* anti-fungal effect of BPI protein products, specifically BPI-derived peptides, in mitigating the total mortality or mortality rate of mice systemically infected with *Candida albicans*. BPI-derived peptides that had been screened for anti-fungal activity in the radial diffusion and broth assays described in Example 1 were prepared as described in Example 1 and purified as follows.

Fungicidal peptides selected for additional studies were synthesized on a large scale. Peptides were made using solid phase peptide synthesis on an Advanced Chemtech (ACT-Model 357 MPS) synthesizer utilizing a 1-Fluorenylmethyl-oxycarbonyl (Fmoc) protection strategy with a double coupling procedure employing N,N-diisopropylcarbodiimide (DIC)/1-hydroxybenzotriazole (HOBt) and 2-(1-H-benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexa-fluorophosphate (HBTU)/HOBt/diisopropylethylamine (DIEA).

The solid support used was a polystyrene resin with 1% divinylbenzene (DVB) cross-linking and an 4-(2′,4′-dimethoxyphenyl-Fmoc-aminomethyl)-phenoxy (Fmoc-Rink amide) linker with a substitution rate of 0.44 mmoles/gram. The scale used was between 0.5 grams and 5 grams of starting resin. Peptides were purified by HPLC, using a Waters Prep LC 2000 Preparative Chromatography System (Water Corp., Milford, MA) equipped with a Delta Pak C-18, 15 um, 300 A cartridge column consisting of a 40 X 10 mm guard cartridge and a 40 X 100 mm Prep Pak cartridge. The column was equilibrated in 25% buffer B, where A=5% acetonitrile/0.1% trifluoroacetic acid and B=80% acetonitrile/0.065% trifluoroacetic acid. Peptides were dissolved to ~20 mg/mL in buffer A and 200-800 mg were applied to the column through the LC pump operating at a flow rate of 8 mL/min. Bound material was eluted with gradient of 25-35% buffer B/30 min

applied at 8 mL/min. (Some peptides were purified with a gradient of 23-33%B/30 min). The eluate was monitored at both 220 and 280 nm with a Waters 490E Programmable Multiwavelength Detector. Fractions were collected and assayed for the peptide of interest on an Ultrafast Micoprotein Analyzer (Michrom BioResources, Inc., Pleasanton, CA) equipped with a Zorbax C-8, 150 X 1 mm, 5 um, 300 A maintained at 40°C. Fractions containing the peptide of interest at >95% purity were pooled and lyophilized to dryness.

Five groups of 15 male DBA/2J mice at age 6-8 weeks (Jackson Laboratory, Bar Habor, ME) were inoculated with 1.24×10^5 *C. albicans* (batch SLU-1 from St. Louis University Medical Center, MO) by intravenous injection into the tail vein. A *Candida* inoculation of 1×10^5 results in an LD_{80} over 28 days in this model. Immediately after fungal challenge, the mice were intravenously injected via the tail vein with 10 mg/kg XMP.36, 5 mg/kg XMP.97, 10 mg/kg XMP.102, 1 mg/kg amphotericin B (Sigma, St. Louis, MO), or 0.1 mL of phosphate buffered saline (PBS) as a control. Treatment with the same amounts of BPI protein products was repeated at Day 2 and Day 4 (except that the second dose of XMP.36 was given at a dose of 5 mg/kg). Mice were monitored twice daily for mortality until termination of the study at Day 28. The mortality data, displayed in Figure 2, show that 100% of the mice treated with amphotericin B survived, 53% of mice treated with XMP.97 survived ($p < 0.05$ compared to control), 33% of mice treated with XMP.36 survived, 27% of mice treated with XMP.102 survived, and 20% of mice treated with PBS survived until Day 28. In Figure 2, the symbol "X" represents survival after treatment with amphotericin B; open squares, treatment with XMP.97; open circles, treatment with XMP.36; open diamonds, treatment with XMP.102; and open triangles, treatment with buffer. Statistical significance was evaluated using the Lifetest Survival Curve analysis. [Lawless, *Statistical Models and Methods for Lifetime Data*, John

Wiley & Sons, New York (1982).] The duration and almost linear decline in survival is analogous to human opportunistic candidiasis.

A second experiment was conducted on five groups of 15 mice, with a fungal challenge of 0.5×10^5 *C. albicans*, followed by treatment at Day 0, Day 2 and Day 5 with 10 mg/kg XMP.127, 5 mg/kg XMP.13, 5 mg/kg XMP.37, 1 mg/kg amphotericin B, or 0.1 mL PBS as a control. The mortality data, displayed in Figure 3, show that 100% of the mice treated with amphotericin B survived, 67% of mice treated with XMP.127 survived ($p < 0.05$ compared to control), 33% of mice treated with XMP.37 survived, 20% of mice treated with XMP.13 survived, and 33% of mice treated with PBS survived until Day 28. In Figure 3, the symbol "X" represents survival after treatment with amphotericin B; open circles, treatment with XMP.127; filled triangles, treatment with buffer; open squares, treatment with XMP.37; open triangles, treatment with XMP.13.

In these studies, amphotericin B was completely protective, as expected. The effect of XMP.102, a control peptide without anti-fungal activity, was no different than PBS. The data demonstrate that administration of BPI-derived peptides XMP.97 and XMP.127 to mice challenged systemically with *C. albicans* unexpectedly provided a significant reduction in mortality compared to buffer-treated controls.

Further experiments are performed to confirm the anti-fungal activity of BPI protein products on strains of *Candida* considered resistant to other anti-fungal agents: polyene-resistant *C. albicans* (ATCC Accession No. 38247), 5-fluorocytosine-resistant *C. albicans* (ATCC No. 44373), azole-resistant *C. albicans* (ATCC No. 62342), and ketoconazole-resistant *C. albicans* (ATCC No. 64124).

Example 3

IN VITRO AND *IN VIVO* EFFECT OF BPI PROTEIN PRODUCTS ON A VARIETY OF FUNGAL SPECIES

The anti-fungal activity of BPI protein products is evaluated *in vitro*, *e.g.*, in broth assays, and *in vivo* in animal models for a variety of fungal species, including *Cryptosporidium parvum*, *Cryptococcus neoformans* and *Histoplasma capsulanum*. Animal models for *C. parvum* include severe combined immunodeficiency (SCID) mouse models and a colostrum-deprived SPF piglet model.

Example 4

IN VIVO ANTI-FUNGAL EFFECT OF BPI PROTEIN PRODUCTS IN *CANDIDA*-INFECTED NEUTROPENIC RATS

This example addresses the *in vivo* testing of BPI protein products for anti-fungal activity, and specifically the efficacy of a BPI protein product, $rBPI_{23}$, in blunting or preventing symptoms of infection and sequelae thereof, including septic shock progression, following infection of neutropenic rats with a massive and lethal dose of a yeast-phase suspension of a clinical isolate of *Candida albicans*. Treatment of the rats with $rBPI_{23}$ (n=6 rats) was compared to treatment with thaumatin (n=5 rats), a control protein having a similar molecular weight and charge but without $rBPI_{23}$'s microbicidal effects. During an initial experiment of overwhelming infection with *Candida* organisms in immunocompromised host animals, animals were monitored for multiple indices including: survival through 24 hours post-infection, systemic arterial pressure, pulse, respiration rate and core temperature, blood cell counts and blood gases, circulating colony-forming units (CFU) of *Candida*, and the microvascular permeability and histopathology of lungs, livers, hearts, and kidneys. Under such conditions of overwhelming infection, treatment with BPI protein may be expected to have little or no effect on survival but may have effects on other indices monitored during infection.

Specifically, the following procedures were followed. Male Sprague-Dawley rats (initial weight = 280-300g, specific pathogen-free; Harlan, Indianapolis, IN) were caged in isolation and permitted free access to food and

water before and during experiments. Absolute neutropenia (defined as a combined segmented and band neutrophil count ≤ 500 PMN/μl) lasting 4-7 days was induced in these animals with 100 mg/kg cyclophosphamide (using a 20 mg/ml solution reconstituted from crystals in sterile phosphate-buffered saline, pH 7.4; Sigma, St. Louis, MO) injected intraperitoneally 4 days prior to infection with *Candida*. On the day before infection, animals were anesthetized with ketamine:xylazine (2:1, 0.9 ml/kg, injected intramuscularly), and the left carotid artery and right jugular vein were aseptically catheterized. Animals received 2.5 mg amikacin sulfate and 300 mg penicillin intravenously immediately after catheterization surgery.

Cultures of *Candida albicans* (CA) of the CA-1 strain were maintained by weekly transfer to Sabouraud dextrose agar slants containing penicillin/streptomycin at 28°C; these were transferred to Sabouraud's broth, incubated at 37°C in a shaking water bath for 48-72 hours, and resuspended in fresh Sabouraud's broth for 24 hours before use. Yeast-phase CA (blastoconidia) for infusions were sedimented at 400 x g for 10 min at 4°C), washed twice in saline, and resuspended in saline to 1 x 10^9 organisms/ml using serial dilutions and a hemacytometer, and kept at 4°C until use. Endotoxin levels in CA infusates were ≤ 30 pg/ml as assayed by a quantitative chromogenic *Limulus* amebocyte lysate assay (Whittaker M.A. Bioproducts, Walkersville, MD). Viability of CA inocula were confirmed by trypan blue exclusion to be >99%, and microscopic examination before use showed no germination. For CA inocula enumerated as 1 x 10^9/ml, the actual colony forming units (CFU) were determined to be 5.7±0.2 x 10^8 CFU/ml (mean ± SEM) by streak-plated serial dilutions on Sabouraud's dextrose agar at 37°C for 24 hours.

Animals were treated with 2 mg/ml solutions of either $rBPI_{23}$ or the control protein, thaumatin (both in 150 mM NaCl, 5 mM Na-citrate, pH 5.0) before and after CA infection. Five minutes before the start of the CA infusion, $rBPI_{23}$ or thaumatin was administered as a 6.6 mg/kg intravenous bolus. The rats were then infected with a massive infusion of organisms over 30 min. (Sage

Pump, Cambridge, MA) [1 x 10^9 CA in 1 ml which yields an LD_{100} in less than 12 hours]. T=0 was considered to be the time at which the CA infusion was completed. Immediately after infection the rats were administered $rBPI_{23}$ or thaumatin as a continuous intravenous infusion of 6.6 mg/kg/hour for 4 hours, followed by a saline infusion of 1 ml/hour for the next 4 hours. Infected animals received additional antibiotics (2.5 mg amikacin sulfate and 300 mg penicillin, intravenously) at T=30 min. after the completion of CA infusion. Six neutropenic control rats were sham-infected with saline and received neither $rBPI_{23}$ nor thaumatin treatment.

Hemodynamic and vital signs were recorded every 30 min. Arterial pressure (mm Hg) and pulse rates (beats/min.) were continuously recorded on a multichannel physiograph (MK-III-S; Narco Bio-Systems, Houston, TX). Respiratory frequency (breaths/min.) was assessed by direct observation, and rectal temperature (°C) was measured by a miniprobe (Diatek, San Diego, CA). A baseline arterial blood sample (1.5 ml) was obtained after a 30 min. equilibration, and additional arterial blood samples were taken at T=1.5 and 4.5 hours (or at death, if occurring earlier). After each blood sample, isovolumetric saline was given via the jugular catheter. These blood samples underwent duplicate analyses of microhematocrit, blood gases using an IL-1306 machine (Instrumentation Laboratory, Lexington, MA), total leukocyte and platelet counts by phase microscopy), differential leukocyte counts (Diff-Quik; Baxter, Miami, FL), and quantitative blood culture (results in Figure 6).

Any animal which exhibited convulsions or increasingly severe respiratory distress was humanely sacrificed and was counted as having survived the previous time point. At death, the cranial lobe of the right lung was excised after bronchial ligation for determination of wet/dry weight ratio (W/D), which is an index of altered microvascular permeability and edema, by drying to constant weight at 70°C. Left lungs were fixed *in situ* with cacodylate-buffered glutaraldehyde for 30 min. at a transpulmonary inflation pressure of 20-22 cm H_2O, followed by fixation of 2-3 mm midlobar slices in fresh glutaraldehyde

overnight at 5°C before dehydration and embedding in paraffin. Serial 6 μm lung sections were stained with hematoxylin and eosin for routine histopathology, periodic acid-Schiff (PAS) to identify yeast, and chloroacetate esterase (CAE) to stain neutrophil granules. Livers, hearts, and kidneys were excised, and standardized tissue sections from these organs were also isolated for W/D determinations, or immersion-fixed in buffered formalin and processed as described above for lung.

Data are presented as means±SEM, with sequential changes for intra- and intergroup variables analyzed by repeated-measures ANOVA and post-hoc comparisons using a Newman-Keuls test. Mortality data were analyzed using Fisher's exact test. Statistical significance was accepted for P-values <0.05.

In this initial experiment, in response to the massive dose of 1 x 10^9 CA, neutropenic rats developed lethal fungemic infection which progressed to shock within 6 hours and which, under these conditions, was not delayed or prevented by treatment with $rBPI_{23}$. It should be noted that the rapid onset of lethal shock in many animals resulted in small n-values at later sampling time points. Although no effect on survival was demonstrated with this dose of 1 x 10^9 CA, these BPI_{23}-treated rats showed statistically significant enhanced intravascular clearance of circulating CA at 1.5 and 4.5 hours relative to animals receiving thaumatin ($p<0.05$; see quantitative blood culture results in Figure 6). Such an anti-fungal effect is surprising and highly significant because reduction of circulating *Candida* levels even by a factor of 10 can be an important factor in therapeutic success.

With this dose of 1 x 10^9 CA organisms, treatment with $rBPI_{23}$ (vs. control protein) did not consistently delay the onset of systemic hypotension and tachypnea with respiratory distress following CA infection. Fungemic circulatory failure in both thaumatin- and $rBPI_{23}$-treated rats was preceded by bradycardia and hypotension which were remarkably abrupt in onset, with the 1 x 10^9 CA-infected animals progressing from hemodynamic stability to death within 15-30 min. Although $rBPI_{23}$ did not prolong survival time among such candidemic animals,

it did attenuate the severe tachypnea (Figure 4) and hypotension (Figure 5) noted by 4.5 hours (or at death, if earlier) in the 1 x 10^9 CA-infected rats treated only with control protein. Thus, $rBPI_{23}$ had unexpected beneficial effects in this model of overwhelming CA infection, by dramatically enhancing the introvascular clearance of circulating organisms as shown in Figure 6 above and by stabilizing both cardiopulmonary indices and vital signs during CA-induced sepsis as shown in Figures 4 and 5. Higher or more sustained doses of BPI protein product are expected to achieve greater beneficial effects in this model. BPI protein product is also expected to provide even better effects at the lower levels of CA seen during relevant clinical CA infection.

Lethal candidemia in thaumatin-treated rats was associated with significant arterial acidemia, hypoxemia, and hypercarbia by death at 3-6 hours. Treatment with $rBPI_{23}$ slightly attenuated both the arterial acidemia (Figure 7) and hypoxemia (Figure 8) during candidemic shock. In all rats studied, the baseline hematological indices of arterial hematocrit, total leukocyte counts, and platelet counts reflected respectively the slight, severe, and moderate decreases induced by cyclophosphamide in this animal model. Higher hematocrits among candidemic rats reflect hemoconcentration due to plasma extravasation, a result which was slightly attenuated by $rBPI_{23}$ treatment when compared to results for candidemic animals receiving the control protein thaumatin. Although total arterial leukocyte counts were low at baseline due to pre-treatment with cyclophosphamide, there was a gradual onset of leukopenia among candidemic rats, and there were no significant differences in leukocyte counts between the $rBPI_{23}$ and thaumatin treatment groups. Finally, all infected rats developed significant arterial thrombocytopenia, which was evident by 4.5 hours (or at death, if earlier) among candidemic animals; treatment with $rBPI_{23}$ did not alter the magnitude or kinetics of peripheral platelet loss compared to thaumatin for any CA-infected group.

Compared to neutropenic control rats which were sham-infected with saline, candidemic rats injected with 1 x 10^9 organisms as described and

treated with either control protein (thaumatin) or BPI protein product ($rBPI_{23}$) had significantly elevated lung wet/dry weight ratios (W/D) but had lesser increases in liver W/D and kidney W/D. Histological examination of lungs from these animals dying of infection by 1 x 10^9 CA revealed that treatment with $rBPI_{23}$ did not alter the rapid development of hemorrhagic pulmonary edema, characterized by severe perivascular and peribronchiolar cuffing and extensive alveolar flooding with fibrin deposition. *Candida* blastoconidia were observed erupting directly into alveolar airspaces from intravascular yeast aggregates as germinating hyphae. Histological changes in the liver were also severe, with hepatocytes showing both complete glycogen depletion and zonal vacuolation with progressive distance from portal triads and adjacent to germinating CA which had been phagocytized but not killed by sinusoidal Kupffer cells. Although other tissues contained germinated yeast as well, notably the heart and kidney, the overall appearance of these organs was unremarkable except for focal masses of CA hyphae.

Example 5

IN VIVO ANTI-FUNGAL EFFECT OF BPI PROTEIN PRODUCTS IN *CANDIDA*-INFECTED NEUTROPENIC RATS

This example addresses additional *in vivo* experiments in view of the beneficial effects of BPI protein product treatment on overwhelming *Candida* infection (i.e., 1 x 10^9 CA organism dose, as described in Example 2) including specifically the significant reduction of *C. albicans* colony-forming units in circulation brought about by BPI protein product administration. Additional experiments are carried out using the neutropenic rat model of *Candida* infection described in Example 2 but wherein lower doses of CA organisms are administered in the animal model and/or increased dosages of BPI protein products are administered, in the same or longer time course, either alone or in combination with known anti-fungal agents. Such experiments are designed to test in a model system designed to more closely approximate typical responses to

casual CA infection, the efficacy of BPI protein products in treating fungal infection, including, e.g., protecting against death and fungemic shock.

Numerous modifications and variations in the practice of the invention are expected to occur to those skilled in the art upon consideration of the foregoing description on the presently preferred embodiments thereof. Consequently the only limitations which should be placed upon the scope of the present invention are those that appear in the appended claims.

SEQUENCE LISTING

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(iii) NUMBER OF SEQUENCES: 227

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(B) COMPUTER: IBM PC compatible
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(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

57

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "Domain I"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Ala Ser Gln Gln Gly Thr Ala Ala Leu Gln Lys Glu Leu Lys Arg Ile
1 5 10 15

Lys Ile Pro Asp Tyr Ser Asp Ser Phe Lys Ile Lys His
20 25

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.14"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Gly Thr Ala Ala Leu Gln Lys Glu Leu Lys Arg Ile Lys Ile Pro Asp
1 5 10 15

Tyr Ser Asp Ser Phe Lys Ile Lys His Leu Gly Lys Gly His
20 25 30

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.4"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Leu Gln Lys Glu Leu Lys Arg Ile Lys Ile Pro Asp Tyr Ser Asp Ser
1 5 10 15

Phe Lys Ile Lys His Leu
20

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.1"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Gln Gln Gly Thr Ala Ala Leu Gln Lys Glu Leu Lys Arg Ile Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.54"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Gly Thr Ala Ala Leu Gln Lys Glu Leu Lys Arg Ile Lys Ile Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "Domain II"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Ser Ser Gln Ile Ser Met Val Pro Asn Val Gly Leu Lys Phe Ser Ile
1 5 10 15

Ser Asn Ala Asn Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg
20 25 30

Phe Leu Lys
35

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.8"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.58"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Cys Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.65 oxidized"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Cys Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

Cys

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.3"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Asn Val Gly Leu Lys Phe Ser Ile Ser Asn Ala Asn Ile Lys Ile Ser
1 5 10 15

Gly Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
20 25

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "Domain III"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Val His Val His Ile Ser Lys Ser Lys Val Gly Trp Leu Ile Gln Leu
1 5 10 15

Phe His Lys Lys Ile Glu Ser Ala Leu Arg Asn Lys
20 25

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.11"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Lys Ser Lys Val Trp Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.12"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Ser Val His Val His Ile Ser Lys Ser Lys Val Gly Trp Leu Ile Gln
1 5 10 15

Leu Phe His Lys Lys Ile Glu Ser Ala Leu Arg Asn Lys
20 25

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.13"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.15"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Ala Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.16"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Ile Ala Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.17"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Ile Lys Ala Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.18"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Ile Lys Ile Ala Gly Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.19"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Ile Lys Ile Ser Ala Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.20"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Ile Lys Ile Ser Gly Ala Trp Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.21"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Ile Lys Ile Ser Gly Lys Ala Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.22"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Ile Lys Ile Ser Gly Lys Trp Ala Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.23"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Ala Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.24"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Ala Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.25"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Ala Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.26"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Ala Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.27"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe Ala Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.28"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe Leu Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.59"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Ile Lys Ile Ser Gly Ala Trp Ala Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.45"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Ala Ala Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.60"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Ile Ala Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe Leu Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.31"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Ala Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.32"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Lys Ala Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.33"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Lys Ser Ala Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.34"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Lys Ser Lys Ala Gly Trp Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.35"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Lys Ser Lys Val Ala Trp Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.36"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

Lys Ser Lys Val Gly Ala Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.37"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

Lys Ser Lys Val Gly Trp Ala Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.38"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Lys Ser Lys Val Gly Trp Leu Ala Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.39"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

Lys Ser Lys Val Gly Trp Leu Ile Ala Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.40"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Lys Ser Lys Val Gly Trp Leu Ile Gln Ala Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.41"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Ala His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.42"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe Ala Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.43"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Ala Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.44"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.56"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Lys Gln Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.61"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Ile Lys Ile Ser Gly Lys Phe Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.66"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 7
(D) OTHER INFORMATION: /label= D-Trp
/note= "The amino acid at position 7 is
D-tryptophan"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.67"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6..8
(D) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 7 is
beta-1-naphthyl-substituted"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Ile Lys Ile Ser Gly Lys Ala Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.9"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Lys Arg Phe Leu Lys Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.30"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys Lys Ser Lys Val Gly Trp
1 5 10 15

Leu Ile Gln Leu Phe His Lys Lys
20

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.63"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys Lys
1 5 10 15

Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
20 25

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.7"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys Lys Trp Lys Ala Gln Lys
1 5 10 15

Arg Phe Leu Lys
20

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.10.1"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Lys Arg Phe Leu Lys Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys Lys
1 5 10 15

Trp Lys Ala Gln Lys Arg Phe Leu Lys
20 25

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.29"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys Lys Ser
1 5 10 15

Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
20 25

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.46"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Lys Trp Lys Ala Ala Ala Arg Phe Leu Lys Lys Trp Lys Ala Gln Lys
1 5 10 15

Arg Phe Leu Lys
20

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.47"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys Lys Trp Lys Ala Ala Ala
1 5 10 15

Arg Phe Leu Lys
20

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.48"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Lys Trp Lys Ala Ala Ala Arg Phe Leu Lys Lys Trp Lys Ala Ala Ala
1 5 10 15

Arg Phe Leu Lys
20

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.69"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Lys Trp Lys Ala Ala Ala Arg Phe Leu Lys Lys Trp Lys Ala Ala Ala
1 5 10 15

Arg Phe Leu Lys Lys Trp Lys Ala Ala Ala Arg Phe Leu Lys
20 25 30

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.55"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Gly Trp Leu Ile Gln Leu Phe His Lys Lys Ile Glu Ser Ala Leu Arg
1 5 10 15

Asn Lys Met Asn Ser
20

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.73"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Phe Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.70"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 8..10
(D) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 7 is
beta-3-pyridyl-substituted"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Ile Lys Ile Ser Gly Lys Ala Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.71"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 13..15
(D) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 13 is
beta-3-pyridyl-substituted"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Ala Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.10.2"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Gln Lys Arg Phe Leu Lys Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
20 25

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.72"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1..3
(D) OTHER INFORMATION: /label= D-alanine
/note= "The position 1 and position 2 alanine residues are both D-alanine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Ala Ala Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe Leu
1 5 10 15
Lys

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.5"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Val His Val His Ile Ser Lys Ser Lys Val Gly Trp Leu Ile Gln Leu
1 5 10 15
Phe His Lys Lys Ile Glu
20

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.65 reduced"

(ix) FEATURE:
(A) NAME/KEY: Disulfide-bond
(B) LOCATION: 1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

Cys Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
1 5 10 15

Cys

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 487 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "rBPI"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Met Arg Glu Asn Met Ala Arg Gly Pro Cys Asn Ala Pro Arg Trp Val
-31 -30 -25 -20

Ser Leu Met Val Leu Val Ala Ile Gly Thr Ala Val Thr Ala Ala Val
-15 -10 -5 1

Asn Pro Gly Val Val Val Arg Ile Ser Gln Lys Gly Leu Asp Tyr Ala
5 10 15

Ser Gln Gln Gly Thr Ala Ala Leu Gln Lys Glu Leu Lys Arg Ile Lys
20 25 30

Ile Pro Asp Tyr Ser Asp Ser Phe Lys Ile Lys His Leu Gly Lys Gly
35 40 45

His Tyr Ser Phe Tyr Ser Met Asp Ile Arg Glu Phe Gln Leu Pro Ser
50 55 60 65

Ser Gln Ile Ser Met Val Pro Asn Val Gly Leu Lys Phe Ser Ile Ser
70 75 80

Asn Ala Asn Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe
85 90 95

Leu Lys Met Ser Gly Asn Phe Asp Leu Ser Ile Glu Gly Met Ser Ile
100 105 110

Ser Ala Asp Leu Lys Leu Gly Ser Asn Pro Thr Ser Gly Lys Pro Thr
115 120 125

Ile Thr Cys Ser Ser Cys Ser Ser His Ile Asn Ser Val His Val His
130 135 140 145

Ile Ser Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
150 155 160

Ile Glu Ser Ala Leu Arg Asn Lys Met Asn Ser Gln Val Cys Glu Lys
165 170 175

Val Thr Asn Ser Val Ser Ser Lys Leu Gln Pro Tyr Phe Gln Thr Leu
180 185 190

Pro Val Met Thr Lys Ile Asp Ser Val Ala Gly Ile Asn Tyr Gly Leu
195 200 205

Val Ala Pro Pro Ala Thr Thr Ala Glu Thr Leu Asp Val Gln Met Lys
210 215 220 225

Gly Glu Phe Tyr Ser Glu Asn His His Asn Pro Pro Pro Phe Ala Pro
230 235 240

Pro Val Met Glu Phe Pro Ala Ala His Asp Arg Met Val Tyr Leu Gly
245 250 255

Leu Ser Asp Tyr Phe Phe Asn Thr Ala Gly Leu Val Tyr Gln Glu Ala
260 265 270

Gly Val Leu Lys Met Thr Leu Arg Asp Asp Met Ile Pro Lys Glu Ser
275 280 285

Lys Phe Arg Leu Thr Thr Lys Phe Phe Gly Thr Phe Leu Pro Glu Val
290 295 300 305

Ala Lys Lys Phe Pro Asn Met Lys Ile Gln Ile His Val Ser Ala Ser
310 315 320

Thr Pro Pro His Leu Ser Val Gln Pro Thr Gly Leu Thr Phe Tyr Pro
325 330 335

Ala Val Asp Val Gln Ala Phe Ala Val Leu Pro Asn Ser Ser Leu Ala
340 345 350

Ser Leu Phe Leu Ile Gly Met His Thr Thr Gly Ser Met Glu Val Ser
355 360 365

Ala Glu Ser Asn Arg Leu Val Gly Glu Leu Lys Leu Asp Arg Leu Leu
370 375 380 385

Leu Glu Leu Lys His Ser Asn Ile Gly Pro Phe Pro Val Glu Leu Leu
390 395 400

Gln Asp Ile Met Asn Tyr Ile Val Pro Ile Leu Val Leu Pro Arg Val
405 410 415

Asn Glu Lys Leu Gln Lys Gly Phe Pro Leu Pro Thr Pro Ala Arg Val
420 425 430

Gln Leu Tyr Asn Val Val Leu Gln Pro His Gln Asn Phe Leu Leu Phe
435 440 445

Gly Ala Asp Val Val Tyr Lys
450 455

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.74"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys Lys Trp
1 5 10 15

Lys Ala Gln Lys Arg Phe Leu Lys
20

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.76"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10..12
(D) OTHER INFORMATION: /label= D-Phe
/note= "The amino acid at position 11 is
D-phenylalanine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Phe Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.77"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Trp Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.79"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Lys Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.80"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10..12
(D) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 11 is
beta-1-naphthyl-substituted"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Ala Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.81"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Phe Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.82"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Trp His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.83"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10..12
(D) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 6 is
beta-1-naphthyl-substituted"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Lys Ser Lys Val Gly Ala Lys Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.84"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6..8
(D) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 7 is
beta-1-naphthyl-substituted"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Ile Lys Ile Ser Gly Lys Ala Lys Ala Gln Phe Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.85"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Lys Ser Lys Val Leu Trp Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.86"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

Lys Ser Lys Val Gly Trp Leu Ile Leu Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.87"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe Leu Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.88"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Phe Phe Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.98"

(ix) FEATURE:.
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(D) OTHER INFORMATION: /label= Substituted-Trp
/note= "The alanine at position 2 is
beta-1-naphthyl-substituted"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

Lys Trp Lys Ala Gln Phe Arg Phe Leu Lys Lys Ser Lys Val Gly Trp
1 5 10 15

Leu Ile Phe Leu Phe His Lys Lys
20

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.89"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6..8
(D) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 7 is
beta-1-naphthyl-substituted"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

Ile Lys Ile Ser Gly Lys Ala Lys Ala Phe Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.90"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6..8
(D) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 7 is
beta-1-naphthyl-substituted"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Ile Lys Ile Ser Gly Lys Ala Lys Ala Phe Phe Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.91"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

Lys Ser Lys Val Gly Trp Leu Ile Phe Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.92"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

Lys Ser Lys Val Gly Trp Leu Ile Lys Leu Phe His Lys Lys

1 5 10

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.93"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6..8
(D) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 7 is
beta-1-naphthyl-substituted"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

Ile Lys Ile Ser Gly Lys Ala Lys Ala Gln Phe Arg Phe Leu Lys Lys
1 5 10 15

Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
20 25

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.94"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe Phe Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.95"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Lys Ser Lys Val Phe Trp Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.96"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Phe
1 5 10

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.97"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

Lys Ser Lys Val Lys Trp Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.99"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

Lys Trp Lys Ala Gln Trp Arg Phe Leu Lys Lys Trp Lys Ala Gln Trp
1 5 10 15

Arg Phe Leu Lys Lys Trp Lys Ala Gln Trp Arg Phe Leu Lys
20 25 30

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.100"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

Lys Ser Lys Val Lys Trp Leu Ile Lys Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.101"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

Lys Ser Lys Val Lys Trp Leu Ile Lys Leu Phe Phe Lys Phe Lys Ser
1 5 10 15

Lys Val Lys Trp Leu Ile Lys Leu Phe Phe Lys Phe
20 25

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.102"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

Lys Trp Lys Ala Gln Phe Arg Phe Leu Lys Lys Ser Lys Val Gly Trp
1 5 10 15

Leu Ile Leu Leu Phe His Lys Lys
20

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1443 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1443.

(ix) FEATURE:
(A) NAME/KEY: mat_peptide
(B) LOCATION: 76..1443

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "rLBP"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

```
ATG GGG GCC TTG GCC AGA GCC CTG CCG TCC ATA CTG CTG GCA TTG CTG      48
Met Gly Ala Leu Ala Arg Ala Leu Pro Ser Ile Leu Leu Ala Leu Leu
-25                 -20                 -15                 -10

CTT ACG TCC ACC CCA GAG GCT CTG GGT GCC AAC CCC GGC TTG GTC GCC      96
Leu Thr Ser Thr Pro Glu Ala Leu Gly Ala Asn Pro Gly Leu Val Ala
            -5                  1                   5

AGG ATC ACC GAC AAG GGA CTG CAG TAT GCG GCC CAG GAG GGG CTA TTG     144
Arg Ile Thr Asp Lys Gly Leu Gln Tyr Ala Ala Gln Glu Gly Leu Leu
        10                  15                  20

GCT CTG CAG AGT GAG CTG CTC AGG ATC ACG CTG CCT GAC TTC ACC GGG     192
Ala Leu Gln Ser Glu Leu Leu Arg Ile Thr Leu Pro Asp Phe Thr Gly
    25                  30                  35

GAC TTG AGG ATC CCC CAC GTC GGC CGT GGG CGC TAT GAG TTC CAC AGC     240
Asp Leu Arg Ile Pro His Val Gly Arg Gly Arg Tyr Glu Phe His Ser
40                  45                  50                  55

CTG AAC ATC CAC AGC TGT GAG CTG CTT CAC TCT GCG CTG AGG CCT GTC     288
Leu Asn Ile His Ser Cys Glu Leu Leu His Ser Ala Leu Arg Pro Val
                60                  65                  70

CCT GGC CAG GGC CTG AGT CTC AGC ATC TCC GAC TCC TCC ATC CGG GTC     336
Pro Gly Gln Gly Leu Ser Leu Ser Ile Ser Asp Ser Ser Ile Arg Val
            75                  80                  85

CAG GGC AGG TGG AAG GTG CGC AAG TCA TTC TTC AAA CTA CAG GGC TCC     384
Gln Gly Arg Trp Lys Val Arg Lys Ser Phe Phe Lys Leu Gln Gly Ser
        90                  95                  100

TTT GAT GTC AGT GTC AAG GGC ATC AGC ATT TCG GTC AAC CTC CTG TTG     432
Phe Asp Val Ser Val Lys Gly Ile Ser Ile Ser Val Asn Leu Leu Leu
    105                 110                 115

GGC AGC GAG TCC TCC GGG AGG CCC ACA GTT ACT GCC TCC AGC TGC AGC     480
Gly Ser Glu Ser Ser Gly Arg Pro Thr Val Thr Ala Ser Ser Cys Ser
120                 125                 130                 135

AGT GAC ATC GCT GAC GTG GAG GTG GAC ATG TCG GGA GAC TTG GGG TGG     528
Ser Asp Ile Ala Asp Val Glu Val Asp Met Ser Gly Asp Leu Gly Trp
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                140                 145                 150
CTG TTG AAC CTC TTC CAC AAC CAG ATT GAG TCC AAG TTC CAG AAA GTA      576
Leu Leu Asn Leu Phe His Asn Gln Ile Glu Ser Lys Phe Gln Lys Val
            155                 160                 165

CTG GAG AGC AGG ATT TGC GAA ATG ATC CAG AAA TCG GTG TCC TCC GAT      624
Leu Glu Ser Arg Ile Cys Glu Met Ile Gln Lys Ser Val Ser Ser Asp
        170                 175                 180

CTA CAG CCT TAT CTC CAA ACT CTG CCA GTT ACA ACA GAG ATT GAC AGT      672
Leu Gln Pro Tyr Leu Gln Thr Leu Pro Val Thr Thr Glu Ile Asp Ser
    185                 190                 195

TTC GCC GAC ATT GAT TAT AGC TTA GTG GAA GCC CCT CGG GCA ACA GCC      720
Phe Ala Asp Ile Asp Tyr Ser Leu Val Glu Ala Pro Arg Ala Thr Ala
200                 205                 210                 215

CAG ATG CTG GAG GTG ATG TTT AAG GGT GAA ATC TTT CAT CGT AAC CAC      768
Gln Met Leu Glu Val Met Phe Lys Gly Glu Ile Phe His Arg Asn His
                220                 225                 230

CGT TCT CCA GTT ACC CTC CTT GCT GCA GTC ATG AGC CTT CCT GAG GAA      816
Arg Ser Pro Val Thr Leu Leu Ala Ala Val Met Ser Leu Pro Glu Glu
            235                 240                 245

CAC AAC AAA ATG GTC TAC TTT GCC ATC TCG GAT TAT GTC TTC AAC ACG      864
His Asn Lys Met Val Tyr Phe Ala Ile Ser Asp Tyr Val Phe Asn Thr
        250                 255                 260

GCC AGC CTG GTT TAT CAT GAG GAA GGA TAT CTG AAC TTC TCC ATC ACA      912
Ala Ser Leu Val Tyr His Glu Glu Gly Tyr Leu Asn Phe Ser Ile Thr
    265                 270                 275

GAT GAG ATG ATA CCG CCT GAC TCT AAT ATC CGA CTG ACC ACC AAG TCC      960
Asp Glu Met Ile Pro Pro Asp Ser Asn Ile Arg Leu Thr Thr Lys Ser
280                 285                 290                 295

TTC CGA CCC TTC GTC CCA CGG TTA GCC AGG CTC TAC CCC AAC ATG AAC     1008
Phe Arg Pro Phe Val Pro Arg Leu Ala Arg Leu Tyr Pro Asn Met Asn
                300                 305                 310

CTG GAA CTC CAG GGA TCA GTG CCC TCT GCT CCG CTC CTG AAC TTC AGC     1056
Leu Glu Leu Gln Gly Ser Val Pro Ser Ala Pro Leu Leu Asn Phe Ser
            315                 320                 325

CCT GGG AAT CTG TCT GTG GAC CCC TAT ATG GAG ATA GAT GCC TTT GTG     1104
Pro Gly Asn Leu Ser Val Asp Pro Tyr Met Glu Ile Asp Ala Phe Val
        330                 335                 340

CTC CTG CCC AGC TCC AGC AAG GAG CCT GTC TTC CGG CTC AGT GTG GCC     1152
Leu Leu Pro Ser Ser Ser Lys Glu Pro Val Phe Arg Leu Ser Val Ala
    345                 350                 355

ACT AAT GTG TCC GCC ACC TTG ACC TTC AAT ACC AGC AAG ATC ACT GGG     1200
Thr Asn Val Ser Ala Thr Leu Thr Phe Asn Thr Ser Lys Ile Thr Gly
360                 365                 370                 375

TTC CTG AAG CCA GGA AAG GTA AAA GTG GAA CTG AAA GAA TCC AAA GTT     1248
Phe Leu Lys Pro Gly Lys Val Lys Val Glu Leu Lys Glu Ser Lys Val
                380                 385                 390
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GGA CTA TTC AAT GCA GAG CTG TTG GAA GCG CTC CTC AAC TAT TAC ATC      1296
Gly Leu Phe Asn Ala Glu Leu Leu Glu Ala Leu Leu Asn Tyr Tyr Ile
            395                 400                 405

CTT AAC ACC TTC TAC CCC AAG TTC AAT GAT AAG TTG GCC GAA GGC TTC      1344
Leu Asn Thr Phe Tyr Pro Lys Phe Asn Asp Lys Leu Ala Glu Gly Phe
        410                 415                 420

CCC CTT CCT CTG CTG AAG CGT GTT CAG CTC TAC GAC CTT GGG CTG CAG      1392
Pro Leu Pro Leu Leu Lys Arg Val Gln Leu Tyr Asp Leu Gly Leu Gln
    425                 430                 435

ATC CAT AAG GAC TTC CTG TTC TTG GGT GCC AAT GTC CAA TAC ATG AGA      1440
Ile His Lys Asp Phe Leu Phe Leu Gly Ala Asn Val Gln Tyr Met Arg
440                 445                 450                 455

GTT
Val                                                              1443
```

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 481 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "rLBP"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

```
Met Gly Ala Leu Ala Arg Ala Leu Pro Ser Ile Leu Leu Ala Leu Leu
-25                 -20                 -15                 -10

Leu Thr Ser Thr Pro Glu Ala Leu Gly Ala Asn Pro Gly Leu Val Ala
                -5                  1                   5

Arg Ile Thr Asp Lys Gly Leu Gln Tyr Ala Ala Gln Glu Gly Leu Leu
        10                  15                  20

Ala Leu Gln Ser Glu Leu Leu Arg Ile Thr Leu Pro Asp Phe Thr Gly
    25                  30                  35

Asp Leu Arg Ile Pro His Val Gly Arg Gly Arg Tyr Glu Phe His Ser
40                  45                  50                  55

Leu Asn Ile His Ser Cys Glu Leu Leu His Ser Ala Leu Arg Pro Val
                60                  65                  70

Pro Gly Gln Gly Leu Ser Leu Ser Ile Ser Asp Ser Ser Ile Arg Val
            75                  80                  85

Gln Gly Arg Trp Lys Val Arg Lys Ser Phe Phe Lys Leu Gln Gly Ser
        90                  95                  100

Phe Asp Val Ser Val Lys Gly Ile Ser Ile Ser Val Asn Leu Leu Leu
    105                 110                 115
```

Gly Ser Glu Ser Ser Gly Arg Pro Thr Val Thr Ala Ser Ser Cys Ser
120 125 130 135

Ser Asp Ile Ala Asp Val Glu Val Asp Met Ser Gly Asp Leu Gly Trp
140 145 150

Leu Leu Asn Leu Phe His Asn Gln Ile Glu Ser Lys Phe Gln Lys Val
155 160 165

Leu Glu Ser Arg Ile Cys Glu Met Ile Gln Lys Ser Val Ser Ser Asp
170 175 180

Leu Gln Pro Tyr Leu Gln Thr Leu Pro Val Thr Thr Glu Ile Asp Ser
185 190 195

Phe Ala Asp Ile Asp Tyr Ser Leu Val Glu Ala Pro Arg Ala Thr Ala
200 205 210 215

Gln Met Leu Glu Val Met Phe Lys Gly Glu Ile Phe His Arg Asn His
220 225 230

Arg Ser Pro Val Thr Leu Leu Ala Ala Val Met Ser Leu Pro Glu Glu
235 240 245

His Asn Lys Met Val Tyr Phe Ala Ile Ser Asp Tyr Val Phe Asn Thr
250 255 260

Ala Ser Leu Val Tyr His Glu Glu Gly Tyr Leu Asn Phe Ser Ile Thr
265 270 275

Asp Glu Met Ile Pro Pro Asp Ser Asn Ile Arg Leu Thr Thr Lys Ser
280 285 290 295

Phe Arg Pro Phe Val Pro Arg Leu Ala Arg Leu Tyr Pro Asn Met Asn
300 305 310

Leu Glu Leu Gln Gly Ser Val Pro Ser Ala Pro Leu Leu Asn Phe Ser
315 320 325

Pro Gly Asn Leu Ser Val Asp Pro Tyr Met Glu Ile Asp Ala Phe Val
330 335 340

Leu Leu Pro Ser Ser Ser Lys Glu Pro Val Phe Arg Leu Ser Val Ala
345 350 355

Thr Asn Val Ser Ala Thr Leu Thr Phe Asn Thr Ser Lys Ile Thr Gly
360 365 370 375

Phe Leu Lys Pro Gly Lys Val Lys Val Glu Leu Lys Glu Ser Lys Val
380 385 390

Gly Leu Phe Asn Ala Glu Leu Leu Glu Ala Leu Leu Asn Tyr Tyr Ile
395 400 405

Leu Asn Thr Phe Tyr Pro Lys Phe Asn Asp Lys Leu Ala Glu Gly Phe
410 415 420

Pro Leu Pro Leu Leu Lys Arg Val Gln Leu Tyr Asp Leu Gly Leu Gln
425 430 435

Ile His Lys Asp Phe Leu Phe Leu Gly Ala Asn Val Gln Tyr Met Arg
440 445 450 455

Val

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.57"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

Cys Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Pro Leu Cys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.75"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

Ile Lys Lys Arg Ala Ile Ser Phe Leu Gly Lys Lys Trp Gln Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.282"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

Lys Trp Lys Ala Phe Phe Arg Phe Leu Lys Lys Trp Lys Ala Phe Phe
1 5 10 15

Arg Phe Leu Lys
20

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.103"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Trp Lys Arg Phe Leu Lys Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.104"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

Lys Ser Lys Val Gly Trp Leu Ile Ser Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.105"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 13
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 13 is beta-1-
naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Trp Lys Arg Ala Leu Lys Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.106"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

Lys Ser Lys Val Gly Trp Leu Ile Thr Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.107"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe Trp Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.108"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Trp
1 5 10

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.109"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 11
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 11 is beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Ala His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.110"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 12
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 12 is beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe Ala Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.111"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 14
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 14 is beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.112"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 7
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 7 is beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 11
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 11 is beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

Ile Lys Ile Ser Gly Lys Ala Lys Ala Gln Ala Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.113"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

Lys Ser Lys Val Gly Trp Leu Ile Gln Phe Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.114"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

Lys Trp Gln Leu Arg Ser Lys Gly Lys Ile Lys Ile Phe Lys Ala
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.116"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 6 is beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

Lys Ser Lys Val Lys Ala Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.119"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 7
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 7 is beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 10 is beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

Ile Lys Ile Ser Gly Lys Ala Lys Ala Ala Lys Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.120"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Lys Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.121"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 10 is beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 11
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 11 is beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Ala Ala Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.122"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 7
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 7 is beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 10 is beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 11
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 11 is beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

Ile Lys Ile Ser Gly Lys Ala Lys Ala Ala Ala Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.123"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 9
(C) OTHER INFORMATION: /label= Substituted-Phe
/note= "The phenylalanine at position 9 is p-amino-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

Lys Ser Lys Val Gly Trp Leu Ile Phe Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.124"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

Lys Ser Lys Val Lys Trp Leu Ile Gln Leu Trp His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.125"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

Lys Ser Lys Val Gly Trp Leu Ile Tyr Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.126"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= D-Trp
/note= "The amino acid at position 6 is
D-tryptophan."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.127"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

Lys Ser Lys Val Gly Phe Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.128"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= D-Phe
/note= "The amino acid at position 6 is
D-phenylalanine."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

Lys Ser Lys Val Gly Phe Leu Ile Gln Leu Pro His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.129"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 6 is
D-1-beta-1-naphthyl-
substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Lys Ser Lys Val Gly Ala Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.130"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 6 is
2-beta-1-naphthyl-
substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

Lys Ser Lys Val Gly Ala Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:127:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.131"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 6 is
D-2-beta-1-naphthyl-
substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

Lys Ser Lys Val Gly Ala Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:128:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.132"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 6 is pyridyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

Lys Ser Lys Val Gly Ala Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.133"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Phe
/note= "The phenylalanine at position 6 is para-amino-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

Lys Ser Lys Val Gly Phe Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.134"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(C) OTHER INFORMATION: /label= Substituted-Phe
/note= "The phenylalanine at position 5 is para-amino-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

Lys Ser Lys Val Phe Trp Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.135"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

Lys Ser Lys Val Gly Lys Leu Ile Gln Leu Pro His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.136"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Glu Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.137"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

Cys Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys Cys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:134:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.138"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

Lys Ser Lys Val Lys Phe Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:135:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.139"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

Lys Ser Lys Val Gly Tyr Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:136:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.140"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 1 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 2 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

Ala Ala Arg Phe Leu Lys Phe
1 5

(2) INFORMATION FOR SEQ ID NO:137:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.141"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Trp Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:138:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.142"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:

Lys Ser Lys Val Gly Trp Leu Ile Gln Trp Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:139:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.143"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 10 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

Lys Ser Lys Val Gly Trp Leu Ile Gln Ala Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:140:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.144"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 6 is
cyclohexyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

Lys Ser Lys Val Gly Ala Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:141:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.145"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:

Lys Trp Lys Ala Ala Ala Arg Phe Leu Lys Lys Ser Lys Val Gly Trp
1 5 10 15

Leu Ile Gln Leu Phe His Lys Lys
20

(2) INFORMATION FOR SEQ ID NO:142:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.146"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 12
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 12 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 14
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 14 is beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe Ala Lys Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:143:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.147"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Glu Lys Lys Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:144:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.148"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 6 is beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 12
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 12 is beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:

Lys Ser Lys Val Gly Ala Leu Ile Gln Leu Phe Ala Lys Lys
1 5 10

105

(2) INFORMATION FOR SEQ ID NO:145:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1813 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 31..1491

(ix) FEATURE:
(A) NAME/KEY: mat_peptide
(B) LOCATION: 124..1491

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "rBPI"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:

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CAGGCCTTGA GGTTTTGGCA GCTCTGGAGG ATG AGA GAG AAC ATG GCC AGG GGC      54
                                 Met Arg Glu Asn Met Ala Arg Gly
                                 -31 -30                  -25

CCT TGC AAC GCG CCG AGA TGG GTG TCC CTG ATG GTG CTC GTC GCC ATA     102
Pro Cys Asn Ala Pro Arg Trp Val Ser Leu Met Val Leu Val Ala Ile
            -20                 -15                 -10

GGC ACC GCC GTG ACA GCG GCC GTC AAC CCT GGC GTC GTG GTC AGG ATC     150
Gly Thr Ala Val Thr Ala Ala Val Asn Pro Gly Val Val Val Arg Ile
        -5                  1                   5

TCC CAG AAG GGC CTG GAC TAC GCC AGC CAG CAG GGG ACG GCC GCT CTG     198
Ser Gln Lys Gly Leu Asp Tyr Ala Ser Gln Gln Gly Thr Ala Ala Leu
 10                  15                  20                  25

CAG AAG GAG CTG AAG AGG ATC AAG ATT CCT GAC TAC TCA GAC AGC TTT     246
Gln Lys Glu Leu Lys Arg Ile Lys Ile Pro Asp Tyr Ser Asp Ser Phe
                30                  35                  40

AAG ATC AAG CAT CTT GGG AAG GGG CAT TAT AGC TTC TAC AGC ATG GAC     294
Lys Ile Lys His Leu Gly Lys Gly His Tyr Ser Phe Tyr Ser Met Asp
            45                  50                  55

ATC CGT GAA TTC CAG CTT CCC AGT TCC CAG ATA AGC ATG GTG CCC AAT     342
Ile Arg Glu Phe Gln Leu Pro Ser Ser Gln Ile Ser Met Val Pro Asn
        60                  65                  70

GTG GGC CTT AAG TTC TCC ATC AGC AAC GCC AAT ATC AAG ATC AGC GGG     390
Val Gly Leu Lys Phe Ser Ile Ser Asn Ala Asn Ile Lys Ile Ser Gly
    75                  80                  85

AAA TGG AAG GCA CAA AAG AGA TTC TTA AAA ATG AGC GGC AAT TTT GAC     438
Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys Met Ser Gly Asn Phe Asp
 90                  95                  100                 105

CTG AGC ATA GAA GGC ATG TCC ATT TCG GCT GAT CTG AAG CTG GGC AGT     486
Leu Ser Ile Glu Gly Met Ser Ile Ser Ala Asp Leu Lys Leu Gly Ser
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                  110                 115                 120

AAC CCC ACG TCA GGC AAG CCC ACC ATC ACC TGC TCC AGC TGC AGC AGC      534
Asn Pro Thr Ser Gly Lys Pro Thr Ile Thr Cys Ser Ser Cys Ser Ser
            125                 130                 135

CAC ATC AAC AGT GTC CAC GTG CAC ATC TCA AAG AGC AAA GTC GGG TGG      582
His Ile Asn Ser Val His Val His Ile Ser Lys Ser Lys Val Gly Trp
        140                 145                 150

CTG ATC CAA CTC TTC CAC AAA AAA ATT GAG TCT GCG CTT CGA AAC AAG      630
Leu Ile Gln Leu Phe His Lys Lys Ile Glu Ser Ala Leu Arg Asn Lys
    155                 160                 165

ATG AAC AGC CAG GTC TGC GAG AAA GTG ACC AAT TCT GTA TCC TCC AAG      678
Met Asn Ser Gln Val Cys Glu Lys Val Thr Asn Ser Val Ser Ser Lys
170                 175                 180                 185

CTG CAA CCT TAT TTC CAG ACT CTG CCA GTA ATG ACC AAA ATA GAT TCT      726
Leu Gln Pro Tyr Phe Gln Thr Leu Pro Val Met Thr Lys Ile Asp Ser
                190                 195                 200

GTG GCT GGA ATC AAC TAT GGT CTG GTG GCA CCT CCA GCA ACC ACG GCT      774
Val Ala Gly Ile Asn Tyr Gly Leu Val Ala Pro Pro Ala Thr Thr Ala
            205                 210                 215

GAG ACC CTG GAT GTA CAG ATG AAG GGG GAG TTT TAC AGT GAG AAC CAC      822
Glu Thr Leu Asp Val Gln Met Lys Gly Glu Phe Tyr Ser Glu Asn His
        220                 225                 230

CAC AAT CCA CCT CCC TTT GCT CCA CCA GTG ATG GAG TTT CCC GCT GCC      870
His Asn Pro Pro Pro Phe Ala Pro Pro Val Met Glu Phe Pro Ala Ala
    235                 240                 245

CAT GAC CGC ATG GTA TAC CTG GGC CTC TCA GAC TAC TTC TTC AAC ACA      918
His Asp Arg Met Val Tyr Leu Gly Leu Ser Asp Tyr Phe Phe Asn Thr
250                 255                 260                 265

GCC GGG CTT GTA TAC CAA GAG GCT GGG GTC TTG AAG ATG ACC CTT AGA      966
Ala Gly Leu Val Tyr Gln Glu Ala Gly Val Leu Lys Met Thr Leu Arg
                270                 275                 280

GAT GAC ATG ATT CCA AAG GAG TCC AAA TTT CGA CTG ACA ACC AAG TTC     1014
Asp Asp Met Ile Pro Lys Glu Ser Lys Phe Arg Leu Thr Thr Lys Phe
            285                 290                 295

TTT GGA ACC TTC CTA CCT GAG GTG GCC AAG AAG TTT CCC AAC ATG AAG     1062
Phe Gly Thr Phe Leu Pro Glu Val Ala Lys Lys Phe Pro Asn Met Lys
        300                 305                 310

ATA CAG ATC CAT GTC TCA GCC TCC ACC CCG CCA CAC CTG TCT GTG CAG     1110
Ile Gln Ile His Val Ser Ala Ser Thr Pro Pro His Leu Ser Val Gln
    315                 320                 325

CCC ACC GGC CTT ACC TTC TAC CCT GCC GTG GAT GTC CAG GCC TTT GCC     1158
Pro Thr Gly Leu Thr Phe Tyr Pro Ala Val Asp Val Gln Ala Phe Ala
330                 335                 340                 345

GTC CTC CCC AAC TCC TCC CTG GCT TCC CTC TTC CTG ATT GGC ATG CAC     1206
Val Leu Pro Asn Ser Ser Leu Ala Ser Leu Phe Leu Ile Gly Met His
                350                 355                 360
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ACA ACT GGT TCC ATG GAG GTC AGC GCC GAG TCC AAC AGG CTT GTT GGA      1254
Thr Thr Gly Ser Met Glu Val Ser Ala Glu Ser Asn Arg Leu Val Gly
            365                 370                 375

GAG CTC AAG CTG GAT AGG CTG CTC CTG GAA CTG AAG CAC TCA AAT ATT      1302
Glu Leu Lys Leu Asp Arg Leu Leu Leu Glu Leu Lys His Ser Asn Ile
        380                 385                 390

GGC CCC TTC CCG GTT GAA TTG CTG CAG GAT ATC ATG AAC TAC ATT GTA      1350
Gly Pro Phe Pro Val Glu Leu Leu Gln Asp Ile Met Asn Tyr Ile Val
    395                 400                 405

CCC ATT CTT GTG CTG CCC AGG GTT AAC GAG AAA CTA CAG AAA GGC TTC      1398
Pro Ile Leu Val Leu Pro Arg Val Asn Glu Lys Leu Gln Lys Gly Phe
410                 415                 420                 425

CCT CTC CCG ACG CCG GCC AGA GTC CAG CTC TAC AAC GTA GTG CTT CAG      1446
Pro Leu Pro Thr Pro Ala Arg Val Gln Leu Tyr Asn Val Val Leu Gln
                430                 435                 440

CCT CAC CAG AAC TTC CTG CTG TTC GGT GCA GAC GTT GTC TAT AAA          1491
Pro His Gln Asn Phe Leu Leu Phe Gly Ala Asp Val Val Tyr Lys
            445                 450                 455

TGAAGGCACC AGGGGTGCCG GGGGCTGTCA GCCGCACCTG TTCCTGATGG GCTGTGGGGC   1551

ACCGGCTGCC TTTCCCCAGG GAATCCTCTC CAGATCTTAA CCAAGAGCCC CTTGCAAACT   1611

TCTTCGACTC AGATTCAGAA ATGATCTAAA CACGAGGAAA CATTATTCAT TGGAAAAGTG   1671

CATGGTGTGT ATTTTAGGGA TTATGAGCTT CTTTCAAGGG CTAAGGCTGC AGAGATATTT   1731

CCTCCAGGAA TCGTGTTTCA ATTGTAACCA AGAAATTTCC ATTTGTGCTT CATGAAAAAA   1791

AACTTCTGGT TTTTTTCATG TG                                            1813
```

(2) INFORMATION FOR SEQ ID NO:146:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 487 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:

```
Met Arg Glu Asn Met Ala Arg Gly Pro Cys Asn Ala Pro Arg Trp Val
-31 -30                 -25                 -20

Ser Leu Met Val Leu Val Ala Ile Gly Thr Ala Val Thr Ala Ala Val
-15                 -10                 -5                  1

Asn Pro Gly Val Val Val Arg Ile Ser Gln Lys Gly Leu Asp Tyr Ala
            5                   10                  15

Ser Gln Gln Gly Thr Ala Ala Leu Gln Lys Glu Leu Lys Arg Ile Lys
        20                  25                  30

Ile Pro Asp Tyr Ser Asp Ser Phe Lys Ile Lys His Leu Gly Lys Gly
    35                  40                  45
```

His Tyr Ser Phe Tyr Ser Met Asp Ile Arg Glu Phe Gln Leu Pro Ser
50 55 60 65

Ser Gln Ile Ser Met Val Pro Asn Val Gly Leu Lys Phe Ser Ile Ser
70 75 80

Asn Ala Asn Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Phe
85 90 95

Leu Lys Met Ser Gly Asn Phe Asp Leu Ser Ile Glu Gly Met Ser Ile
100 105 110

Ser Ala Asp Leu Lys Leu Gly Ser Asn Pro Thr Ser Gly Lys Pro Thr
115 120 125

Ile Thr Cys Ser Ser Cys Ser Ser His Ile Asn Ser Val His Val His
130 135 140 145

Ile Ser Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
150 155 160

Ile Glu Ser Ala Leu Arg Asn Lys Met Asn Ser Gln Val Cys Glu Lys
165 170 175

Val Thr Asn Ser Val Ser Ser Lys Leu Gln Pro Tyr Phe Gln Thr Leu
180 185 190

Pro Val Met Thr Lys Ile Asp Ser Val Ala Gly Ile Asn Tyr Gly Leu
195 200 205

Val Ala Pro Pro Ala Thr Thr Ala Glu Thr Leu Asp Val Gln Met Lys
210 215 220 225

Gly Glu Phe Tyr Ser Glu Asn His His Asn Pro Pro Pro Phe Ala Pro
230 235 240

Pro Val Met Glu Phe Pro Ala Ala His Asp Arg Met Val Tyr Leu Gly
245 250 255

Leu Ser Asp Tyr Phe Phe Asn Thr Ala Gly Leu Val Tyr Gln Glu Ala
260 265 270

Gly Val Leu Lys Met Thr Leu Arg Asp Asp Met Ile Pro Lys Glu Ser
275 280 285

Lys Phe Arg Leu Thr Thr Lys Phe Phe Gly Thr Phe Leu Pro Glu Val
290 295 300 305

Ala Lys Lys Phe Pro Asn Met Lys Ile Gln Ile His Val Ser Ala Ser
310 315 320

Thr Pro Pro His Leu Ser Val Gln Pro Thr Gly Leu Thr Phe Tyr Pro
325 330 335

Ala Val Asp Val Gln Ala Phe Ala Val Leu Pro Asn Ser Ser Leu Ala
340 345 350

Ser Leu Phe Leu Ile Gly Met His Thr Thr Gly Ser Met Glu Val Ser
355 360 365

Ala Glu Ser Asn Arg Leu Val Gly Glu Leu Lys Leu Asp Arg Leu Leu
370 375 380 385

Leu Glu Leu Lys His Ser Asn Ile Gly Pro Phe Pro Val Glu Leu Leu
390 395 400

Gln Asp Ile Met Asn Tyr Ile Val Pro Ile Leu Val Leu Pro Arg Val
405 410 415

Asn Glu Lys Leu Gln Lys Gly Phe Pro Leu Pro Thr Pro Ala Arg Val
420 425 430

Gln Leu Tyr Asn Val Val Leu Gln Pro His Gln Asn Phe Leu Leu Phe
435 440 445

Gly Ala Asp Val Val Tyr Lys
450 455

(2) INFORMATION FOR SEQ ID NO:147:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.149"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:

Lys Trp Lys Val Phe Lys Lys Ile Glu Lys Lys Ser Lys Val Gly Trp
1 5 10 15

Leu Ile Gln Leu Phe His Lys Lys
20

(2) INFORMATION FOR SEQ ID NO:148:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.150"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:148:

Lys Trp Ala Phe Ala Lys Lys Gln Lys Lys Arg Leu Lys Arg Gln Trp
1 5 10 15

Leu Lys Lys Phe
20

(2) INFORMATION FOR SEQ ID NO:149:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 amino acids
(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.153"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:149:

Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys Lys Trp Lys Ala Gln Lys
1 5 10 15

Arg Phe Leu Lys Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys
20 25 30

(2) INFORMATION FOR SEQ ID NO:150:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.154"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 5 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:150:

Lys Trp Lys Ala Ala Ala Arg Phe Leu Lys Lys Trp Lys Ala Gln Lys
1 5 10 15

Arg Phe Leu Lys
20

(2) INFORMATION FOR SEQ ID NO:151:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature

(D) OTHER INFORMATION: "XMP.155"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 15
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 15 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 16
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 16 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:151:

Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys Lys Trp Lys Ala Ala Ala
1 5 10 15

Arg Phe Leu Lys
20

(2) INFORMATION FOR SEQ ID NO:152:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.156"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 5 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 15
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 15 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 16
(C) OTHER INFORMATION: /label= Substituted-Ala

/note= "Position 16 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:152:

Lys Trp Lys Ala Ala Ala Arg Phe Leu Lys Lys Trp Lys Ala Ala Ala
1 5 10 15

Arg Phe Leu Lys
20

(2) INFORMATION FOR SEQ ID NO:153:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.157"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 5 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 15
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 15 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 16
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 16 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 25
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 25 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 26

(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 26 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:153:

Lys Trp Lys Ala Ala Ala Arg Phe Leu Lys Lys Trp Lys Ala Ala Ala
1 5 10 15

Arg Phe Leu Lys Lys Trp Lys Ala Ala Ala Arg Phe Leu Lys
20 25 30

(2) INFORMATION FOR SEQ ID NO:154:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.158"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 10 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 11
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 11 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:154:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Ala Ala Arg Phe Leu Lys Lys
1 5 10 15

Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
20 25

(2) INFORMATION FOR SEQ ID NO:155:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.159"

(ix) FEATURE:
(A) NAME/KEY: Modified-site

(B) LOCATION: 2
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 2 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:155:

Lys Ala Lys Ala Gln Ala Arg Phe Leu Lys Lys Ser Lys Val Gly Trp
1 5 10 15

Leu Ile Gln Leu Trp His Lys Lys
20

(2) INFORMATION FOR SEQ ID NO:156:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.160"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 2 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 12
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 12 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 16
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 16 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:156:

Lys Ala Lys Ala Gln Ala Arg Phe Leu Lys Lys Ala Lys Ala Gln Ala
1 5 10 15

Arg Phe Leu Lys
20

(2) INFORMATION FOR SEQ ID NO:157:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.161"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:157:

Lys Ser Lys Val Lys Ala Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:158:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.162"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:158:

Lys Trp Lys Ala Gln Trp Arg Phe Leu Lys Lys Ser Lys Val Gly Trp
1 5 10 15

Leu Ile Gln Leu Phe His Lys Lys
20

(2) INFORMATION FOR SEQ ID NO:159:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.163"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:159:

Lys Trp Lys Ala Gln Trp Arg Phe Leu Lys Lys Trp Lys Ala Gln Trp
1 5 10 15

Arg Phe Leu Lys
20

(2) INFORMATION FOR SEQ ID NO:160:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.164"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 5 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 15
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 15 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:160:

Lys Trp Lys Ala Ala Lys Arg Phe Leu Lys Lys Trp Lys Ala Ala Lys
1 5 10 15

Arg Phe Leu Lys
20

(2) INFORMATION FOR SEQ ID NO:161:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.165"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 2 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 12
(C) OTHER INFORMATION: /label= Substituted-Ala

/note= "Position 12 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:161:

Lys Ala Lys Ala Gln Phe Arg Phe Leu Lys Lys Ala Lys Ala Gln Phe
1 5 10 15

Arg Phe Leu Lys
20

(2) INFORMATION FOR SEQ ID NO:162:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.166"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:162:

Lys Ser Lys Val Gly Val Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:163:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.167"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:163:

Lys Trp Lys Ala Gln Lys Arg Phe
1 5

(2) INFORMATION FOR SEQ ID NO:164:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.168"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:164:

Cys Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys Met Ser Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:165:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.169"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:165:

Cys Lys Trp Lys Ala Gln Lys Arg Phe Cys
1 5 10

(2) INFORMATION FOR SEQ ID NO:166:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.221"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 13
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 13 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:166:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Gln Lys Arg Ala Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:167:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.222"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6

(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 14
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 14 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:167:

Lys Ser Lys Val Gly Ala Leu Ile Gln Leu Phe His Lys Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:168:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.223"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 10 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:168:

Lys Ser Lys Val Gly Ala Leu Ile Gln Ala Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:169:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.224"

(ix) FEATURE:

(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 9
(C) OTHER INFORMATION: /label= Substituted-Phe
/note= "Position 9 is
para-amino-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:169:

Lys Ser Lys Val Gly Ala Leu Ile Phe Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:170:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.225"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(C) OTHER INFORMATION: /label= Substituted-Phe
/note= "Position 5 is
para-amino-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:170:

Lys Ser Lys Val Phe Ala Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:171:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.226"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:171:

Lys Ser Lys Val Gly Ala Leu Ile Gln Leu Trp His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:172:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.227"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 10 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 14
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 14 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:172:

Lys Ser Lys Val Gly Trp Leu Ile Gln Ala Phe His Lys Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:173:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.228"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 9
(C) OTHER INFORMATION: /label= Substituted-Phe
/note= "Position 9 is

para-amino-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 14
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 14 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:173:

Lys Ser Lys Val Gly Trp Leu Ile Phe Leu Phe His Lys Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:174:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.229"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 5 is
para-amino-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 14
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 14 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:174:

Lys Ser Lys Val Phe Trp Leu Ile Gln Leu Phe His Lys Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:175:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.230"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 14

(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 14 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:175:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Trp His Lys Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:176:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.231"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 10 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 12
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 12 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:176:

Lys Ser Lys Val Gly Trp Leu Ile Gln Ala Phe Ala Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:177:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.232"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 9
(C) OTHER INFORMATION: /label= Substituted-Phe
/note= "Position 9 is
para-amino-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site

(B) LOCATION: 12
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 12 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:177:

Lys Ser Lys Val Gly Trp Leu Ile Phe Leu Phe Ala Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:178:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.233"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(C) OTHER INFORMATION: /label= Substituted-Phe
/note= "Position 5 is
para-amino-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 12
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 12 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:178:

Lys Ser Lys Val Phe Trp Leu Ile Gln Leu Phe Ala Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:179:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.234"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 12
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 12 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:179:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Trp Ala Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:180:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.235"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 9
(C) OTHER INFORMATION: /label= Substituted-Phe
/note= "Position 9 is
para-amino-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 10 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:180:

Lys Ser Lys Val Gly Trp Leu Ile Phe Ala Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:181:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.236"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(C) OTHER INFORMATION: /label= Substituted-Phe
/note= "Position 5 is
para-amino-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 10 is

beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:181:

Lys Ser Lys Val Phe Trp Leu Ile Gln Ala Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:182:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.237"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 10 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:182:

Lys Ser Lys Val Gly Trp Leu Ile Gln Ala Trp His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:183:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.238"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(C) OTHER INFORMATION: /label= Substituted-Phe
/note= "Position 5 is
para-amino-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 9
(C) OTHER INFORMATION: /label= Substituted-Phe
/note= "Position 9 is
para-amino-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:183:

Lys Ser Lys Val Phe Trp Leu Ile Phe Leu Phe His Lys Lys

1 5 10

(2) INFORMATION FOR SEQ ID NO:184:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.239"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 9
(C) OTHER INFORMATION: /label= Substituted-Phe
/note= "Position 9 is
para-amino-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:184:

Lys Ser Lys Val Gly Trp Leu Ile Phe Leu Trp His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:185:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.240"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(C) OTHER INFORMATION: /label= Substituted-Phe
/note= "Position 5 is
para-amino-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:185:

Lys Ser Lys Val Phe Trp Leu Ile Gln Leu Trp His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:186:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.247"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 2 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:186:

Lys Ala Lys Ala Gln Ala Arg Phe Leu Lys Lys Ser Lys Val Gly Trp
1 5 10 15

Leu Ile Leu Leu Phe His Lys Lys
20

(2) INFORMATION FOR SEQ ID NO:187:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.245"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:187:

Lys Trp Lys Ala Gln Phe Arg Phe Leu Lys Lys Ser Lys Val Gly Trp
1 5 10 15

Leu Ile Gln Leu Trp His Lys Lys
20

(2) INFORMATION FOR SEQ ID NO:188:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.246"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 16

(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 16 is
D-beta-2-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:188:

Lys Trp Lys Ala Gln Phe Arg Phe Leu Lys Lys Ser Lys Val Gly Ala
1 5 10 15

Leu Ile Gln Leu Phe His Lys Lys
20

(2) INFORMATION FOR SEQ ID NO:189:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.248"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 2 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
beta-1-naphthyl-substituted."

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 16
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 16 is
D-beta-2-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:189:

Lys Ala Lys Ala Gln Ala Arg Phe Leu Lys Lys Ser Lys Val Gly Ala
1 5 10 15

Leu Ile Gln Leu Phe His Lys Lys
20

(2) INFORMATION FOR SEQ ID NO:190:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.242"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
D-beta-2-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:190:

Lys Ser Lys Val Gly Ala Leu Ile Leu Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:191:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.272"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:191:

Lys Ser Lys Val Gly Trp Leu Ile Leu Leu Phe His Lys Lys Lys Ser
1 5 10 15

Lys Val Gly Trp Leu Ile Leu Leu Phe His Lys Lys
20 25

(2) INFORMATION FOR SEQ ID NO:192:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.275"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:192:

Lys Ser Lys Val Gly Trp Leu Ile Phe Leu Phe His Lys Lys Lys Ser
1 5 10 15

Lys Val Gly Trp Leu Ile Phe Leu Phe His Lys Lys
20 25

(2) INFORMATION FOR SEQ ID NO:193:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.270"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:193:

Lys Ser Lys Val Gly Trp Leu Ile Leu Leu Phe His Lys Lys Lys Ser
1 5 10 15

Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
20 25

(2) INFORMATION FOR SEQ ID NO:194:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.271"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:194:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys Lys Ser
1 5 10 15

Lys Val Gly Trp Leu Ile Leu Leu Phe His Lys Lys
20 25

(2) INFORMATION FOR SEQ ID NO:195:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.273"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:195:

Lys Ser Lys Val Gly Trp Leu Ile Phe Leu Phe His Lys Lys Lys Ser
1 5 10 15

Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys
20 25

(2) INFORMATION FOR SEQ ID NO:196:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.274"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:196:

Lys Ser Lys Val Gly Trp Leu Ile Gln Leu Phe His Lys Lys Lys Ser
1 5 10 15

Lys Val Gly Trp Leu Ile Phe Leu Phe His Lys Lys
20 25

(2) INFORMATION FOR SEQ ID NO:197:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.276"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:197:

Lys Trp Lys Ala Gln Phe Arg Phe Leu Lys Lys Ser Lys Val Gly Trp
1 5 10 15

Leu Ile Phe Leu Phe His Lys Lys
20

(2) INFORMATION FOR SEQ ID NO:198:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.241"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:198:

Lys Ser Lys Val Gly Trp Leu Ile Leu Leu Trp His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:199:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.243"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
D-beta-2-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:199:

Lys Ser Lys Val Gly Ala Leu Ile Gln Leu Trp His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:200:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.244"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "Position 6 is
D-beta-2-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:200:

Lys Ser Lys Val Gly Ala Leu Ile Leu Leu Trp His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:201:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.249"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:201:

Lys Ser Lys Val Gly Gly Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:202:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.250"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:202:

Lys Ser Lys Val Gly Leu Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:203:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.251"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:203:

Lys Ser Lys Val Gly Ile Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:204:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.252"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /label= D-Ala
/note= "The amino acid at position 6 is
D-alanine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:204:

Lys Ser Lys Val Gly Ala Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:205:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.253"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /label= D-Val
/note= "The amino acid at position 6 is D-valine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:205:

Lys Ser Lys Val Gly Val Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:206:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.254"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /label= beta-Ala
/note= "The amino acid at position 6 is beta-alanine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:206:

Lys Ser Lys Val Gly Ala Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:207:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.255"

(ix) FEATURE:

(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /label= delta-aba
/note= "The amino acid at position 6 is
delta-aminobutyric acid"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:207:

Lys Ser Lys Val Gly Xaa Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:208:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.256"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /label= gaba
/note= "The amino acid at position 6 is
gamma-aminobutyric acid"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:208:

Lys Ser Lys Val Gly Xaa Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:209:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.257"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /label= d-methyl-A
/note= "The amino acid at position 6 is
delta-Methyl-alanine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:209:

Lys Ser Lys Val Gly Ala Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:210:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.258"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /label= t-butyl-G
/note= "The amino acid at position 6 is
tert-butyl-glycine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:210:

Lys Ser Lys Val Gly Gly Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:211:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.259"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /label= N-methyl-G
/note= "The amino acid at position 6 is
N-Methyl-glycine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:211:

Lys Ser Lys Val Gly Gly Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:212:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.260"

(ix) FEATURE:

(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /label= N-methyl-V
/note= "The amino acid at position 6 is N-Methyl-valine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:212:

Lys Ser Lys Val Gly Val Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:213:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.261"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /label= N-methyl-L
/note= "The amino acid at position 6 is N-Methyl-leucine"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:213:

Lys Ser Lys Val Gly Leu Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:214:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.262"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:214:

Lys Ser Lys Val Gly Trp Leu Ile Asn Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:215:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.263"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:215:

Lys Ser Lys Val Gly Trp Leu Ile Glu Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:216:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.264"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:216:

Lys Ser Lys Val Gly Trp Leu Ile Asp Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:217:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.265"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:217:

Lys Ser Lys Val Gly Trp Leu Ile Lys Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:218:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.266"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:218:

Lys Ser Lys Val Lys Val Leu Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:219:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.267"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:219:

Lys Ser Lys Val Lys Trp Ala Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:220:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.268"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:220:

Lys Ser Lys Val Gly Val Ala Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:221:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.269"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:221:

Lys Ser Lys Val Lys Val Ala Ile Gln Leu Phe His Lys Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO:222:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.277"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 2
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 2 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:222:

Lys Ala Lys Ala Gln Phe Arg Phe Leu Lys Lys Ser Lys Val Gly Trp
1 5 10 15

Leu Ile Leu Leu Phe His Lys Lys
20

(2) INFORMATION FOR SEQ ID NO:223:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.278"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:223:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Ala Trp Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:224:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.279"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 10 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:224:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Ala Phe Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:225:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.280"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:225:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Ala Phe Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:226:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.281"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(C) OTHER INFORMATION: /label= Substituted-Ala
/note= "The alanine at position 10 is
beta-1-naphthyl-substituted."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:226:

Ile Lys Ile Ser Gly Lys Trp Lys Ala Ala Ala Arg Phe Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:227:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: misc_feature
(D) OTHER INFORMATION: "XMP.170"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:227:

Lys Trp Lys Ala Gln Lys Arg Phe Leu Lys Met Ser
1 5 10

WHAT IS CLAIMED ARE: 143

1. A method of treating fungal infections comprising administering to a subject suffering from a fungal infection a therapeutically effective amount of a BPI protein product.

2. The method of claim 1 wherein the BPI protein product is an N-terminal fragment of BPI or dimeric form thereof.

3. The method of claim 3 wherein the N-terminal fragment has a molecular weight of approximately between 21 kD and 25 kD.

4. The method of claim 1 wherein the BPI protein product is BPI holoprotein, $rBPI_{23}$ or $rBPI_{21}$.

5. The method of claim 1 wherein the BPI protein product is a BPI-derived peptide having an amino acid sequence of BPI protein from about position 142 to about position 169, subsequences thereof and variants of the sequence or subsequence thereof, which possess anti-fungal activity.

6. The method of claim 1 wherein the fungal infection involves a fungal species selected from the group consisting of *Candida, Aspergillosis, and Cryptococcus* species.

7. The method of claim 6 wherein the fungal species is *C. albicans*.

8. The method of claim 1 wherein the BPI protein product is administered intravenously.

9. The method of claim 1 wherein the BPI protein product is administered as an aerosol.

10. The method of claim 1 comprising the additional step of administering a non-BPI anti-fungal agent.

11. Use of a BPI protein product for the manufacture of a medicament for treatment of fungal infection.

12. Use of a BPI protein product in combination with other anti-fungal agents for the manufacture of a medicament for treatment of fungal infection.

13. A method of killing or inhibiting replication of fungi comprising contacting the fungi with a BPI protein product.

14. The method of claim 13 further comprising contacting the fungal species with an anti-fungal agent.

15. The method of claim 5 wherein the BPI protein product is a BPI-derived peptide selected from the group consisting of XMP.97 (SEQ. ID NO: 92) and XMP.127 (SEQ. ID NO: 123).

Figure 1

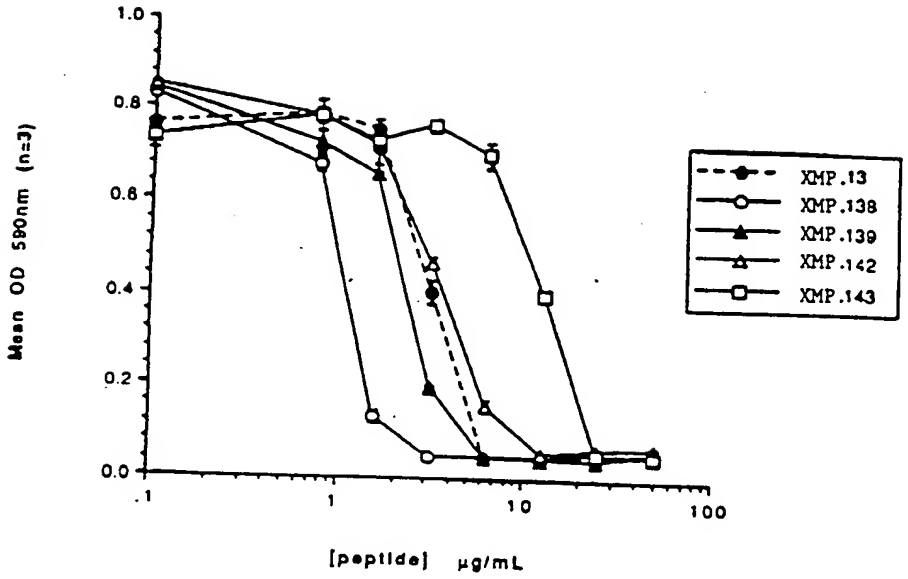

1.0
0.8
0.6
0.4
0.2
0.0
Mean OD 590nm (n=3)
.1
1
10
100
[peptide] µg/mL
XMP.13
XMP.138
XMP.139
XMP.142
XMP.143

Figure 2

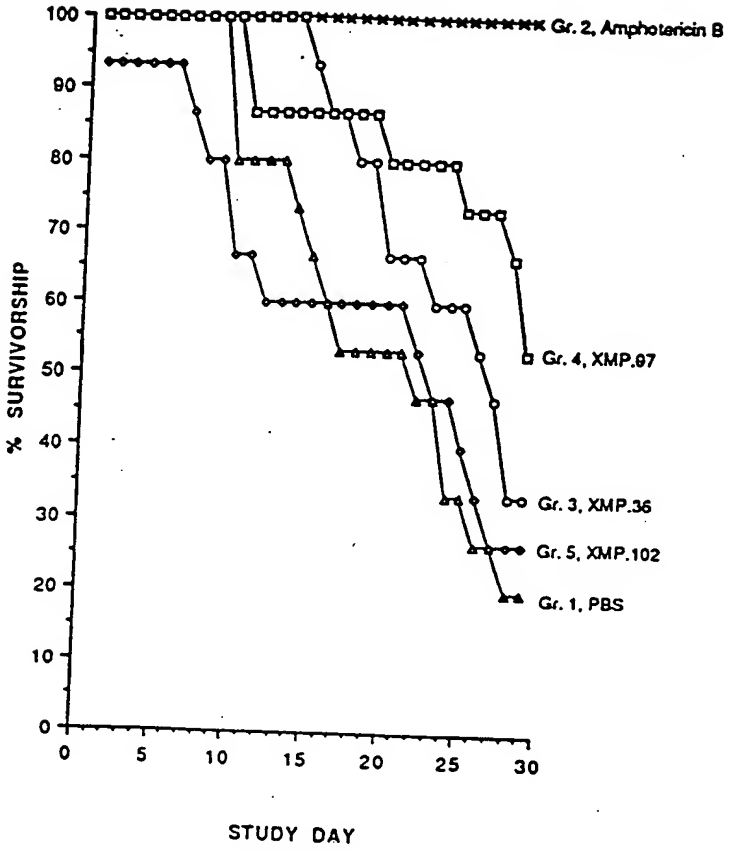

Gr. 2, Amphotericin B
Gr. 4, XMP.97
Gr. 3, XMP.36
Gr. 5, XMP.102
Gr. 1, PBS
% SURVIVORSHIP
STUDY DAY
0
10
20
30
40
50
60
70
80
90
100
0
5
10
15
20
25
30

Figure 3

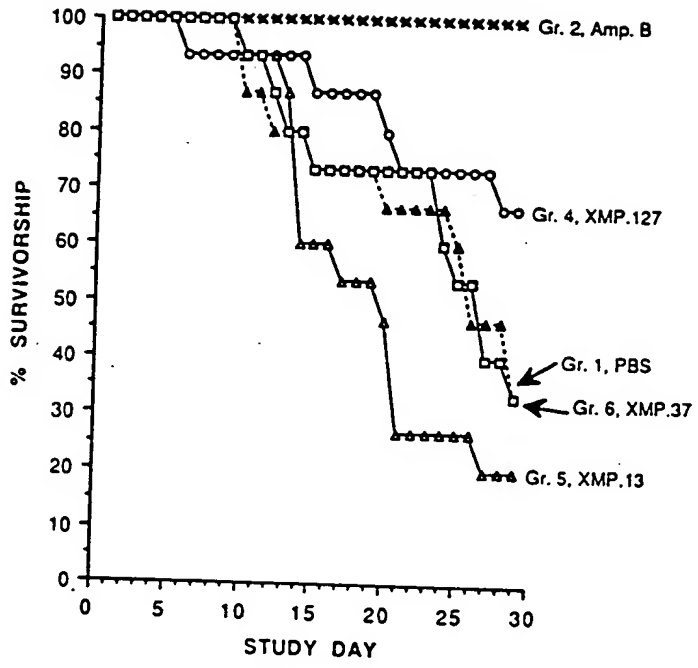

% SURVIVORSHIP
STUDY DAY
Gr. 2, Amp. B
Gr. 4, XMP.127
Gr. 1, PBS
Gr. 6, XMP.37
Gr. 5, XMP.13

Figure 4

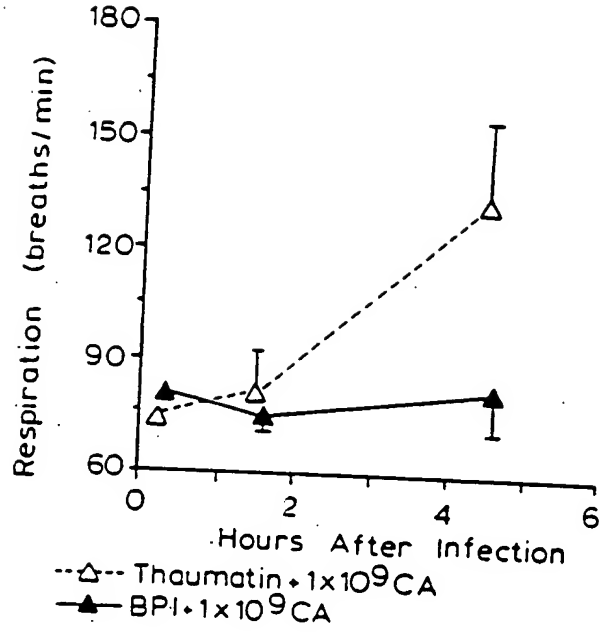


Figure 5

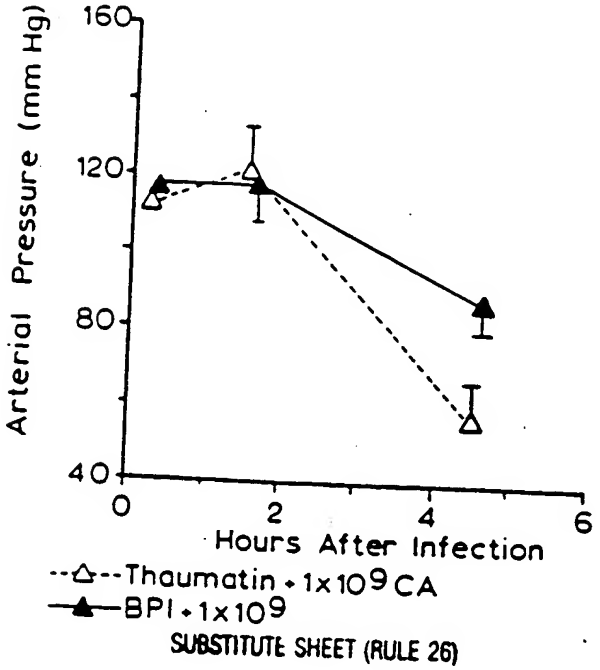


Figure 6

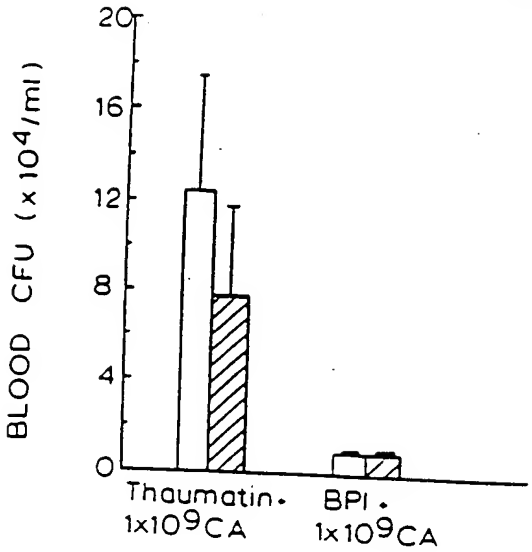


Figure 7

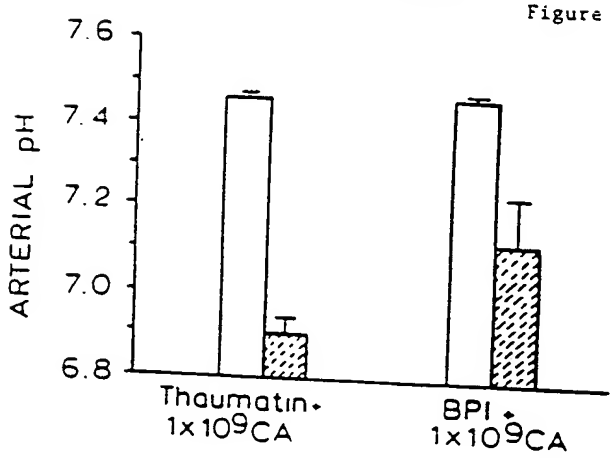
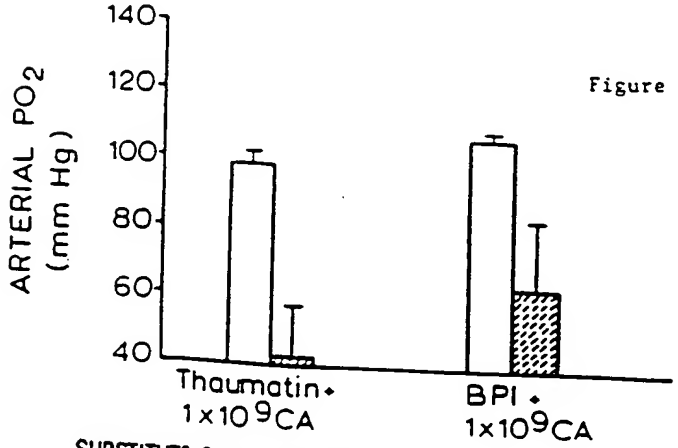


Figure 8



INTERNATIONAL SEARCH REPORT

Interna ul Application No
PCT/US 95/00498

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/17 //C07K14/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,90 09183 (INVITRON CORPORATION) 23 August 1990 see the whole document ---	1-15
P,X	WO,A,94 20532 (XOMA CORPORATION) 15 September 1994 see the whole document -----	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 May 1995	29.05.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Moreau, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

nternational application No.
PCT/US95/00498

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 1-10 and 13-15 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 95/00498

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9009183	23-08-90	US-A-	5089274	18-02-92
		AU-B-	647734	31-03-94
		AU-A-	5170690	05-09-90
		EP-A-	0460058	11-12-91
		JP-T-	4506510	12-11-92
		US-A-	5171739	15-12-92
		US-A-	5234912	10-08-93
		US-A-	5334584	02-08-94
		US-A-	5308834	03-05-94
WO-A-9420532	15-09-94	US-A-	5348942	20-09-94
		AU-B-	6360594	26-09-94
		AU-B-	6398894	26-09-94
		WO-A-	9420128	15-09-94